CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040145

Trade Name : WARFARIN SODIUM TABLETS USP

Generic Name: Warfarin Sodium Tablets USP 1mg, 2mg, 2.5mg, 4mg, 5mg, 7.5mg and 10mg

Sponsor : Barr Laboratories. Inc.

Approval Date: March 26, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040145

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	**X**			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	**X**			
Medical Review(s)				
Chemistry Review(s)	**X**			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	**X**			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040145

APPROVAL LETTER

ANDA 40-145

MAR 26 1997

Barr Laboratories, Inc.
Attention: Ms. Christine A. Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519

Dear Madam:

This is in reference to your abbreviated new drug application dated May 10, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Warfarin Sodium Tablets USP, 1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg and 10 mg.

Reference is also made to your amendments dated May 16, October 2, October 3, November 1, and December 13, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Warfarin Sodium Tablets USP, 1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg and 10 mg tablets to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Coumadin® Tablets, 1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg and 10 mg tablets of Dupont Merck Pharmaceutical Co.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

3/25/97

Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

cc: ANDA #40-145
ANDA #40-145/Division File
Field Copy
HFD-600/Reading File
HFD-92
HFD-610/J.Phillips
HFD-8/P.Savino

Endorsements:

HFD-625/S.Sherken/1-10-97 1/28/97
HFD-613/C.Holquist/1-24-97 1/27/97
HFD-613/J.Grace/1-24-97 1/27/97
HFD-625/M.Smela/1-10-97 1/28/97
HFD-617/S.O'Keefe, PM/1-25-97 1/27/97
X:\NEW\FIRMSAM\BARR\LTRS&REV\40145.APL
F/T by MM January 24, 1997
Approval Letter

1/30/97

Satisfactory pending acceptable QA review.

CMC Audit is satisfactory as the DS and the DP meet USP 23 specifications. However a petition is pending at CBD level

1/30/97

3/21/97

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040145

CHEMISTRY REVIEWS

1. CHEMISTRY REVIEW NO 3

2. ANDA 40-145

3. NAME AND ADDRESS OF APPLICANT

Barr Laboratories, Inc.
Pomona, NY 10970-0519

4. LEGAL BASIS FOR SUBMISSION

505(j)(4)(D) of the act.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Warfarin Sodium Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

DOA 5/10/95; RTFL 6/20/95; Amend 6/26/95; AFF 6/27/95; Bio DL 12/6/95; NA (Major) 2/1/96; Bio Amend 1/25/96; Amend (Major) 3/21/96; Bio Amend 5/16/96; NA 7/26/96; NC 8/23/96; *Amend (Minor) 10/2/96; *NC 10/3/96; Deficiency bio letter 10/28/96; Label review 10/17/96; *NC (Bio) 11/1/96; Consultation reviewed by Medical officer for an IND submission from Barr, 11/4/96; Tel Memos 11/21/96; 11/22/96; *Tele Amendment 12/13/96*; Bio review 12/2/97.

* New amendmentS.

10. PHARMACOLOGICAL CATEGORY

Anticoagulant

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM	14. POTENCY
Pink, Oval, flat faced, beveled edged, scored tablets with **"barr"** on one side and **"555/831*"** on the scored side.	1 mg
Lavender, Oval, flat faced, beveled edged, scored tablets with **"barr"** on one side and **"555/869"*** on the scored side.	2 mg
Green, Oval, flat faced, beveled edged, scored tablets with **"barr"** on one side and **"555/832"*** on the scored side.	2.5 mg
Blue, Oval, flat faced, beveled edged, scored tablets with **"barr"** on one side and **"555/874"*** on the scored side.	4 mg
Peach, Oval, flat faced, beveled edged, scored tablets with **"barr"** on one side and **"555/833"*** on the scored side.	5 mg
Yellow, Oval, flat faced, beveled edged, scored tablets with **"barr"** on one side and **"555/834"*** on the scored side.	7.5 mg
White, Oval, flat faced, beveled edged, scored tablets with **"barr"** on one side and **"555/835"*** on the other side.	10 mg

***Note: Barr changed back to the original debossing configuration of each tablet strength. See review of deficiency #4 below, and review #1 for original debossing.**

15. CHEMICAL NAME AND STRUCTURE

See review #1

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Responses to the four chemistry deficiencies are satisfactory. However on 12/13/96 a new problem was addressed.

On December 13, 1996 Barr provided a validated test and specifications for for the Drug Product. The specification is based on the labeled amount of Warfarin. Barr proposed a specification of f label claim for release and of label claim for stability. This is based on he assumption of as the lower limit in the drug substance.

Labeling found adequate on 10/29/96.

Bio found the in-vivo and in-vitro data adequate on 1/2/97.

EER dated 7/25/96 remains outstanding. EER acceptable 1/25/97 S. Sherken 1/28/97 M Smela - 1/28/97

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 40-145 is approvable, pending satisfactory EER.

19. REVIEWER: DATE COMPLETED:

cc: ANDA #40-145
ANDA #40-145/Division File
Field Copy

Endorsements:

HFD-625/S.Sherken/1-9-97 Stephen Sherken 1/28/97

HFD-625/M.Smela/1-10-97 M Smela 1/28/97

X:\NEW\FIRMSAM\BARR\LTRS&REV\40145A.RV3
F/T MM January 24, 1997
Approval Letter

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040145

FINAL PRINTED LABELING

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.

Protect from light.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R2-96

BARR LABORATORIES, INC.

NDC 0555-0834-02

Warfarin Sodium Tablets, USP
7.5 mg

HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in package brochure. **Caution:** Federal law prohibits dispensing without prescription.

100 Tablets

0555-0834-02

Exp. Date:

Lot No.:

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.

Protect from light.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R2-96

BARR LABORATORIES, INC.

NDC 0555-0834-05

Warfarin Sodium Tablets, USP
7.5 mg

HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in package brochure.
Caution: Federal law prohibits dispensing without prescription.

1000 Tablets

0555-0834-05

Exp. Date:

Lot No.:

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.

Protect from light.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R2-96

BARR LABORATORIES, INC.

NDC 0555-0835-02

Warfarin Sodium Tablets, USP
10 mg

HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in package brochure. **Caution:** Federal law prohibits dispensing without prescription.

100 Tablets

0555-0835-02

Exp. Date:

Lot No.:

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.

Protect from light.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R2-96

BARR LABORATORIES, INC.

NDC 0555-0835-04

Warfarin Sodium Tablets, USP
10 mg

HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in package brochure.

Caution: Federal law prohibits dispensing without prescription.

500 Tablets

0555-0835-04

Exp. Date:

Lot No.:

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.

Protect from light.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R2-96

BARR LABORATORIES, INC.

Warfarin Sodium Tablets, USP

5 mg

HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in package brochure. **Caution:** Federal law prohibits dispensing without prescription.

100 Tablets

NDC 0555-0833-02

Exp. Date: Sample

Lot No.:

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.

Protect from light.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R8-96

BARR LABORATORIES, INC.

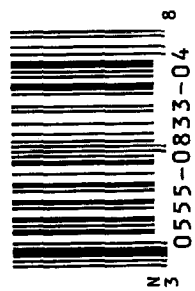
Warfarin Sodium Tablets, USP

5 mg

HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in package brochure.
Caution: Federal law prohibits dispensing without prescription.

500 Tablets

NDC 0555-0833-04



SAMPLE

Exp. Date:

Lot No.:

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.

Protect from light.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R2-96

BARR LABORATORIES, INC.

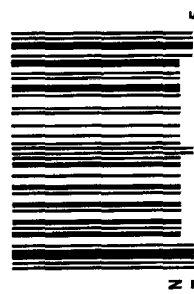
Warfarin Sodium Tablets, USP

5 mg

HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in package brochure.
Caution: Federal law prohibits dispensing without prescription.

1000 Tablets

NDC 0555-0833-05



Exp. Date: Sample

Lot No.:

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.

Protect from light.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R2-96

BARR LABORATORIES, INC.

Warfarin Sodium Tablets, USP
4 mg

HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in package brochure. **Caution:** Federal law prohibits dispensing without prescription.

100 Tablets

NDC 0555-0874-02

0555-0874-02

Exp. Date:

Lot No.

Sample

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.

Protect from light.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R2-96

BARR LABORATORIES, INC.

Warfarin Sodium Tablets, USP 4 mg

HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in package brochure.
Caution: Federal law prohibits dispensing without prescription.

1000 Tablets

NDC 0555-0874-05

0555-0874-05

Exp. Date:

Lot No.:

Sample

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.

Protect from light.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R2-96

BARR LABORATORIES, INC.

Warfarin Sodium Tablets, USP
2.5 mg

HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in package brochure. **Caution:** Federal law prohibits dispensing without prescription.

100 Tablets

NDC 0555-0832-02

Exp. Date:

Lot No.:

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.

Protect from light.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R8-96

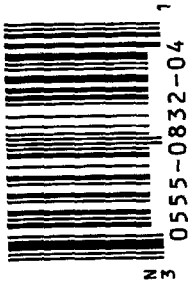
BARR LABORATORIES, INC.

Warfarin Sodium Tablets, USP
2.5 mg

HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in package brochure. **Caution:** Federal law prohibits dispensing without prescription.

500 Tablets

NDC 0555-0832-04



SAMPLE

Exp. Date:

Lot No.:

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.

Protect from light.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R2-96

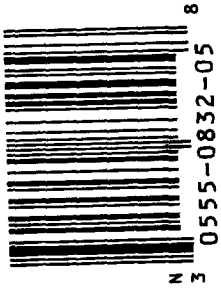
BARR LABORATORIES, INC.

Warfarin Sodium Tablets, USP
2.5 mg

HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in package brochure. **Caution:** Federal law prohibits dispensing without prescription.

1000 Tablets

NDC 0555-0832-05



Exp. Date:

Lot No.:

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.

Protect from light.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R2-96

BARR LABORATORIES, INC.

Warfarin Sodium Tablets, USP

2 mg

HIGHLY POTENT ANTICOAGULANT WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in package brochure. **Caution:** Federal law prohibits dispensing without prescription.

100 Tablets

NDC 0555-0869-02

0555-0869-02

Exp. Date:

Lot No.:

Sample

2 6 1997

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.

Protect from light.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R8-96

BARR LABORATORIES, INC.

Warfarin Sodium Tablets, USP

2 mg

HIGHLY POTENT ANTICOAGULANT WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in package brochure. **Caution:** Federal law prohibits dispensing without prescription.

500 Tablets

NDC 0555-0869-04

0555-0869-04

SAMPLE

Exp. Date:

Lot No.:

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.

Protect from light.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R2-96

BARR LABORATORIES, INC.

Warfarin Sodium Tablets, USP

2 mg

HIGHLY POTENT ANTICOAGULANT WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in package brochure. **Caution:** Federal law prohibits dispensing without prescription.

1000 Tablets

NDC 0555-0869-05

0555-0869-05

Exp. Date:

Lot No.:

Sample

2 6 1997

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.

Protect from light.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R2-96

BARR LABORATORIES, INC.

Warfarin Sodium Tablets, USP
1 mg

HIGHLY POTENT ANTICOAGULANT WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in package brochure. **Caution:** Federal law prohibits dispensing without prescription.

60 Tablets

NDC 0555-0831-02

0555-0831-02

Exp. Date:

Lot No.:

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.

Protect from light.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R8-96

BARR LABORATORIES, INC.

Warfarin Sodium Tablets, USP
1 mg

HIGHLY POTENT ANTICOAGULANT WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in package brochure. **Caution:** Federal law prohibits dispensing without prescription.

500 Tablets

NDC 0555-0831-04

0555-0831-04

SAMPLE

Exp. Date:

Lot No.:

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.

Protect from light.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R2-96

BARR LABORATORIES, INC.

Warfarin Sodium Tablets, USP
1 mg

HIGHLY POTENT ANTICOAGULANT WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in package brochure. **Caution:** Federal law prohibits dispensing without prescription.

1000 Tablets

NDC 0555-0831-05

0555-0831-05

Exp. Date:

Lot No.:

[redacted]

WARFARIN SODIUM TABLETS, USP

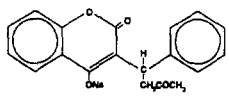
SAMPLE

Revised SEPTEMBER 1996
1008310101

APPROVED
MAY 26 1997

DESCRIPTION:

Warfarin sodium is an anticoagulant which acts by inhibiting vitamin K-dependent coagulation factors. Chemically, it is 3-(α-acetonylbenzyl)-4-hydroxycoumarin and is a racemic mixture of the R and S enantiomers. Warfarin sodium is an isopropanol clathrate. The crystallization of warfarin sodium virtually eliminates trace impurities present in amorphous warfarin. Its structural formula may be represented as follows:



$C_{19}H_{15}NaO_4$ Molecular Weight: 330.31

Warfarin sodium occurs as a white, odorless, crystalline powder, is discolored by light and is very soluble in water; freely soluble in alcohol; very slightly soluble in chloroform and in ether.

Each tablet, for oral administration, contains 1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg or 10 mg warfarin sodium. In addition, each tablet contains the following inactive ingredients: Anhydrous lactose, hydroxypropyl methylcellulose 2208, magnesium stearate, and pregelatinized starch.

The 1 mg also contains D&C red no. 6 barium lake.

The 2 mg also contains FD&C blue no. 2 aluminum lake, and FD&C red no. 40 aluminum lake.

The 2.5 mg also contains D&C yellow no. 10 aluminum lake, and FD&C blue no. 1 aluminum lake.

The 4 mg also contains FD&C blue no. 1 aluminum lake.

The 5 mg also contains FD&C yellow no. 6 aluminum lake.

The 7.5 mg also contains D&C yellow no. 10 aluminum lake, and FD&C yellow no. 6 aluminum lake.

The 10 mg does not contain any dyes.

CLINICAL PHARMACOLOGY:

Warfarin sodium and other coumarin anticoagulants act by inhibiting the synthesis of vitamin K dependent clotting factors, which include Factors II, VII, IX, and X, and the anticoagulant proteins C and S. Half-lives of these clotting factors are as follows: Factor II - 60 hours, VII - 4 to 6 hours, IX - 24 hours, and X - 48 to 72 hours. The half-lives of proteins C and S are approximately 8 hours and 30 hours, respectively. The resultant *in vivo* effect is a sequential depression of Factors VII, IX, X, and II activities. Vitamin K is an essential cofactor for the post ribosomal synthesis of the vitamin K dependent clotting factors. The vitamin promotes the biosynthesis of γ-carboxyglutamic acid residues in the proteins which are essential for biological activity. Warfarin is thought to interfere with clotting factor synthesis by inhibition of the regeneration of vitamin K_1 epoxide. The degree of depression is dependent upon the dosage administered. Therapeutic doses of warfarin decrease the total amount of the active form of each vitamin K dependent clotting factor made by the liver by approximately 30% to 50%.

An anticoagulation effect generally occurs within 24 hours after drug administration. However, peak anticoagulant effect may be delayed 72 to 96 hours. The duration of action of a single dose of racemic warfarin is 2 to 5 days. The effects of warfarin sodium may become more pronounced as effects of daily maintenance doses overlap. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombus has occurred, the goal of anticoagulant treatment is to prevent further extension of the formed clot and prevent secondary thromboembolic complications which may result in serious and possibly fatal sequelae.

Pharmacokinetics:

Warfarin sodium is a racemic mixture of the R- and S-enantiomers. The S-enantiomer exhibits 2 to 5 times more anticoagulant activity than the R-enantiomer in humans, but generally has a more rapid clearance.

Absorption:

Warfarin sodium is essentially completely absorbed after oral administration with peak concentration generally attained within the first 4 hours.

Distribution:

There are no differences in the apparent volumes of distribution after intravenous and oral administration of single doses of warfarin solution. Warfarin distributes into a relatively small apparent volume of distribution of about 0.14 liter/kg. Warfarin distributes into a phase lasting 6 to 12 hours is distinguishable after oral administration of rapid intravenous or oral administration of an aqueous solution. Using a one compartment model, and assuming complete bioavailability, estimates of the volumes of distribution of R- and S-warfarin are similar to each other and to that of the racemate. Concentrations in fetal plasma approach the maternal values, but warfarin has not been found in human milk (see **WARNINGS, Lactation**). Approximately 99% of the drug is bound to plasma proteins.

Metabolism:

The elimination of warfarin is almost entirely by metabolism. Warfarin sodium is stereoselectively metabolized by hepatic microsomal enzymes (cytochrome P-450) to inactive hydroxylated metabolites (predominant route) and by reductases to reduced metabolites (warfarin alcohols). The warfarin alcohols have minimal anticoagulant activity. The metabolites are principally excreted into the urine and to a lesser extent into the bile. The metabolites of warfarin that have been identified include dehydrowarfarin, two diastereoisomer alcohols, 4'-, 6-, 7-, 8- and 10-hydroxywarfarin. The Cytochrome P-450 isozymes involved in the metabolism of warfarin include 2C9, 2C19, 2C8, 2C18, 1A2, and 3A4. 2C9 is likely to be the principal form of human liver P-450 which modulates the *in vivo* anticoagulant activity of warfarin.

Excretion:

The terminal half-life of warfarin after a single dose is approximately one week; however, the effective half-life ranges from 20 to 60 hours, with a mean of about 40 hours. The clearance of R-warfarin is generally half that of S-warfarin, thus as the volumes of distribution are similar, the half-life of R-warfarin is longer than that of S-warfarin. The half-life of R-warfarin ranges from 37 to 89 hours, while that of S-warfarin ranges from 21 to 43 hours. Studies with radiolabeled drug have demonstrated that up to 92% of the orally administered dose is recovered in urine. Very little warfarin is excreted unchanged in urine. Urinary excretion is in the form of metabolites.

Absorption:

Warfarin sodium is essentially completely absorbed after oral administration with peak concentration generally attained within the first 4 hours.

Distribution:

There are no differences in the apparent volumes of distribution after intravenous and oral administration of single doses of warfarin solution. Warfarin distributes into a relatively small apparent volume of distribution of about 0.14 liter/kg. Warfarin distributes into a phase lasting 6 to 12 hours is distinguishable after oral administration of rapid intravenous or oral administration of an aqueous solution. Using a one compartment model, and assuming complete bioavailability, estimates of the volumes of distribution of R- and S-warfarin are similar to each other and to that of the racemate. Concentrations in fetal plasma approach the maternal values, but warfarin has not been found in human milk (see **WARNINGS, Lactation**). Approximately 99% of the drug is bound to plasma proteins.

Metabolism:

The elimination of warfarin is almost entirely by metabolism. Warfarin sodium is stereoselectively metabolized by hepatic microsomal enzymes (cytochrome P-450) to inactive hydroxylated metabolites (predominant route) and by reductases to reduced metabolites (warfarin alcohols). The warfarin alcohols have minimal anticoagulant activity. The metabolites are principally excreted into the urine; and to a lesser extent into the bile. The metabolites of warfarin that have been identified include dehydrowarfarin, two diastereoisomer alcohols, 4'- 6-, 7-, 8- and 10-hydroxywarfarin. The Cytochrome P-450 isozymes involved in the metabolism of warfarin include 2C9, 2C19, 2C8, 2C18, 1A2, and 3A4. 2C9 is likely to be the principal form of human liver P-450 which modulates the *in vivo* anticoagulant activity of warfarin.

Excretion:

The terminal half-life of warfarin after a single dose is approximately one week; however, the effective half-life ranges from 20 to 60 hours, with a mean of about 40 hours. The clearance of R-warfarin is generally half that of S-warfarin, thus as the volumes of distribution are similar, the half-life of R-warfarin is longer than that of S-warfarin. The half-life of R-warfarin ranges from 37 to 89 hours, while that of S-warfarin ranges from 21 to 43 hours. Studies with radiolabeled drug have demonstrated that up to 92% of the orally administered dose is recovered in urine. Very little warfarin is excreted unchanged in urine. Urinary excretion is in the form of metabolites.

Elderly:

There are no significant age-related differences in the pharmacokinetics of racemic warfarin. Limited information suggests that there is no difference in the clearance of S-warfarin in elderly versus young subjects. However, there may be a slight decrease in the clearance of R-warfarin in the elderly compared to the young. Older patients (60 years or older) appear to exhibit greater than expected PT/INR response to the anticoagulant effects of warfarin. As patient age increases, less warfarin is required to produce a therapeutic level of anticoagulation. The cause of this response to warfarin is not known.

Renal Dysfunction:

Renal clearance is considered to be a minor determinant of anticoagulant response to warfarin. No dosage adjustment is necessary for patients with renal failure.

Hepatic Dysfunction:

Hepatic dysfunction can potentiate the response to warfarin through impaired synthesis of clotting factors and decreased metabolism of warfarin.

The administration of warfarin sodium via the intravenous (I.V.) route should provide the patient with the same concentration of an equal oral dose, but maximum plasma concentration will be reached earlier. However, the full anticoagulant effect of a dose of warfarin may not be achieved until 72 to 96 hours after dosing, indicating that the administration of I.V. warfarin sodium should not provide any increased biological effect or earlier onset of action.

Clinical Trials:

Atrial Fibrillation (AF): In five prospective randomized controlled clinical trials involving 3711 patients with non-rheumatic AF, warfarin significantly reduced the risk of systemic thromboembolism including stroke (see Table 1). The risk reduction ranged from 60% to 86% in all except one trial (CAFA: 45%) which stopped early due to published positive results from two of these trials. The incidence of major bleeding in these trials ranged from 0.6 to 2.7% (see Table 1). Meta-analysis findings of these studies revealed that the effects of warfarin in reducing thromboembolic events including stroke were similar at either moderately high INR (2.0 to 4.5) or low INR (1.4 to 3.0). There was a significant reduction in minor bleeds at the low INR. Similar data from clinical studies in valvular atrial fibrillation patients are not available.

TABLE 1
CLINICAL STUDIES OF WARFARIN IN NON-RHEUMATIC AF PATIENTS*

Study	N		PT Ratio	INR	Thromboembolism % Risk Reduction	*p* value	% Major Bleeding	
	Warfarin-Treated Patients	Control Patients					Warfarin-Treated Patients	Control Patients
AFASAK	335	336	1.5-2.0	2.8-4.2	60	0.027	0.6	0.0
SPAF	210	211	1.3-1.8	2.0-4.5	67	0.01	1.9	1.9
BAATAF	212	208	1.2-1.5	1.5-2.7	86	<0.05	0.9	0.5
CAFA	187	191	1.3-1.6	2.0-3.0	45	0.25	2.7	0.5
SPINAF	260	265	1.2-1.5	1.4-2.8	79	0.001	2.3	1.5

*All study results of warfarin vs. control are based on intention-to-treat analysis and include ischemic stroke and systemic thromboembolism, excluding hemorrhage and transient ischemic attacks.

Myocardial Infarction: WARIS (The Warfarin Re-Infarction Study) was a double-blind, randomized study of 1214 patients 2 to 4 weeks post-infarction treated with warfarin to a target INR of 2.8 to 4.8. (But note that a lower INR was achieved and increased bleeding was associated with INR's above 4.0; see **DOSAGE AND ADMINISTRATION.**) The primary endpoint was a combination of total mortality and recurrent infarction. A secondary endpoint of cerebrovascular events was assessed. Mean follow-up of the patients was 37 months. The results for each endpoint separately, including an analysis of vascular death, are provided in the following table:

Event	Warfarin (N=607)		Placebo (N=607)		RR(95
Total Patient Years of Follow-up	2018		1944		
Total Mortality	94 (4.7/100 py)		123 (6.3/100 py)		0.76 (0.6
Vascular Death	82 (4.1/100 py)		105 (5.4/100 py)		0.78 (0.6
Recurrent MI	82 (4.1/100 py)		124 (6.4/100 py)		0.66 (0.5
Cerebrovascular Event	20 (1.0/100 py)		44 (2.3/100 py)		0.46 (0.2

RR=Relative risk; Risk reduction(%) = (RR); CI=Confidence interval; MI=Myocardial in
py=patient years

Major Bleeding Warfarin-Related Events	Control Patients
0.0	
1.9	
0.5	
0.5	
1.5	

Systemic thromboem-

Myocardial Infarction: WARIS (The Warfarin Re-Infarction Study) was a double-blind, randomized study of 1214 patients 2 to 4 weeks post-infarction treated with warfarin to a target INR of 2.8 to 4.8. (But note that a lower INR was achieved and increased bleeding was associated with INR's above 4.0; see **DOSAGE AND ADMINISTRATION**.) The primary endpoint was a combination of *total mortality* and *recurrent infarction*. A secondary endpoint of cerebrovascular events was assessed. Mean follow-up of the patients was 37 months. The results for each endpoint separately, including an analysis of vascular death, are provided in the following table.

Event	Warfarin (N=607)	Placebo (N=607)	RR(95%CI)	% Risk Reduction (p-value)
Total Patient Years of Follow-up	2018	1944		
Total Mortality	94 (4.7/100 PY)	123 (6.3/100 PY)	0.76 (0.60, 0.97)	24 (p=0.030)
Vascular Death	82 (4.1/100 PY)	105 (5.4/100 PY)	0.78 (0.60, 1.02)	22 (p=0.068)
Recurrent MI	82 (4.1/100 PY)	124 (6.4/100 PY)	0.66 (0.51, 0.85)	34 (p=0.001)
Cerebrovascular Event	20 (1.0/100 PY)	44 (2.3/100 PY)	0.46 (0.28, 0.75)	54 (p=0.002)

RR=Relative risk; Risk reduction=(1 - RR); CI=Confidence interval; MI=Myocardial Infarction; PY=patient years

Mechanical and Bioprosthetic Heart Valves: In a prospective, randomized, open label, positive-controlled study (Mok *et al*, 1985) *in 254 patients*, the thromboembolic-free interval was found to be significantly greater in patients with mechanical prosthetic heart valves treated with warfarin alone compared with dipyridamole-aspirin (p<0.005) and pentoxifylline-aspirin (p<0.05) treated patients. Rates of thromboembolic events in these groups were 2.2, 8.6, and 7.9/100 patient years, respectively. Major bleeding rates were 2.5, 0.0, and 0.9/100 patient years, respectively.

In a prospective, open label, clinical trial (Saour et al, 1990) comparing moderate (INR 2.65) vs. high intensity (INR 9.0) warfarin therapies in 258 patients with mechanical prosthetic heart valves, thromboembolism occurred with similar frequency in the two groups (4.0 and 3.7 events/100 patient years, respectively). Major bleeding was more common in the high intensity group (2.1 events/100 patient years) vs. 0.95 events/100 patient years in the moderate intensity group.

In a randomized trial (Turpie et al, 1988) in 210 patients comparing two intensities of warfarin therapy (INR 2.0 to 2.25 *vs.* INR 2.5 to 4.0) for a three month period following tissue heart valve replacement, thromboembolism occurred with similar frequency in the two groups (major embolic events 2.0% vs. 1.9%, respectively and minor embolic events 10.8% vs. 10.2%, respectively). Major bleeding complications were more frequent with the higher intensity (*major hemorrhages 4.6%*) *vs.* none in the lower intensity.

INDICATIONS AND USAGE:

Warfarin sodium tablets are indicated *for the prophylaxis and/or treatment* of venous thrombosis and its extension, and pulmonary embolism.

Warfarin sodium tablets are indicated for the prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement.

Warfarin sodium tablets are indicated to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction.

CONTRAINDICATIONS:

Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than the potential clinical benefits of anticoagulation, such as:

Pregnancy: Warfarin sodium is contraindicated in women who are or may become pregnant because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus *in utero*. Furthermore, there have been *reports of birth malformations* in children born to mothers who have been treated with warfarin during pregnancy.

Embryopathy characterized by nasal hypoplasia with or without stippled epiphyses (chondrodysplasia punctata) has been reported in pregnant women exposed to warfarin during the first trimester. Central nervous system abnormalities also have been reported, including dorsal midline dysplasia characterized by agenesis of the corpus callosum, Dandy-Walker malformation, and midline cerebellar atrophy. Ventral midline dysplasia, characterized by optic atrophy, *and eye abnormalities* have been observed. Mental retardation, blindness, and other central nervous system abnormalities have been reported in association with second and third trimester exposure. Although rare, teratogenic reports following *in utero* exposure to warfarin include urinary tract anomalies such as single kidney, asplenia, anencephaly, spina bifida, *cranial nerve palsy*, hydrocephalus, cardiac defects and congenital heart disease, polydactyly, deformities of toes, diaphragmatic hernia, corneal leukoma, cleft palate, cleft lip, schizencephaly, and microcephaly.

Spontaneous abortion and still birth are known to occur and a higher risk of fetal mortality is associated with the use of warfarin. Low birth weight and growth retardation have also been reported.

Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking *this drug*, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias.

Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces.

Bleeding tendencies associated with active ulceration or overt bleeding of: (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms-cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) bacterial endocarditis.

Threatened abortion, eclampsia and preeclampsia.

Inadequate laboratory facilities.

Unsupervised patients with senility, alcoholism, or psychosis or other lack of patient cooperation.

Spinal puncture and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding.

Miscellaneous: major regional, lumbar block anesthesia, malignant hypertension and known hypersensitivity to warfarin or to any other components of this product.

WARNINGS:

The most serious risks associated with anticoagulant therapy with sodium warfarin are hemorrhage in any tissue or organ and, less frequently (<0.1%), necrosis and/or gangrene of skin and other tissues. The *risk of hemorrhage* is related to the level of intensity and the duration of anticoagulant therapy. Hemorrhage and necrosis have in some cases been reported to result in death or permanent disability. Necrosis appears to be associated with local thrombosis and usually appears within a few days of the start of anticoagulant therapy. In severe cases of necrosis, treatment through debridement or amputation of the affected tissue, limb, breast or penis has been reported. Careful diag*nosis is required* to determine whether necrosis is caused by an underlying disease. Warfarin therapy should be discontinued when warfarin is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation. Although various treatments have been attempted, no treatment for necrosis has been con*sidered uniformly effective. See below for information* on predisposing conditions. These and other risks associated with anticoagulant therapy must be weighed against the risk of thrombosis or embolization in untreated cases.

It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Warfarin sodium, a narrow therapeutic range (index) drug, may be affected by factors such as other drugs and dietary Vitamin K. Dosage should be controlled by periodic determinations of prothrombin time (PT)/International Normalized Ratio

WARNINGS:

The most serious risks associated with anticoagulant therapy with sodium warfarin are hemorrhage in any tissue or organ and, less frequently (<0.1%), necrosis and/or gangrene of skin and other tissues. The risk of hemorrhage is related to the level of intensity and the duration of anticoagulant therapy. Hemorrhage and necrosis have in some cases been reported to result in death or permanent disability. Necrosis appears to be associated with local thrombosis and usually appears within a few days of the start of anticoagulant therapy. In severe cases of necrosis, treatment through debridement or amputation of the affected tissue, limb, breast or penis has been reported. Careful diagnosis is required to determine whether necrosis is caused by an underlying disease. Warfarin therapy should be discontinued when warfarin is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation. Although various treatments have been attempted, no treatment for necrosis has been considered uniformly effective. See below for information on predisposing conditions. These and other risks associated with anticoagulant therapy must be weighed against the risk of thrombosis or embolization in untreated cases.

It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Warfarin sodium, a narrow therapeutic range (index) drug, may be affected by factors such as other drugs and dietary Vitamin K. Dosage should be controlled by periodic determinations of prothrombin time (PT)/International Normalized Ratio (INR) or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage PT. When heparin and warfarin sodium are administered concomitantly, refer below to **Conversion From Heparin Therapy** *for recommendations.*

Caution should be observed when warfarin sodium is administered in any situation or in the presence of any predisposing condition where added risk of hemorrhage or necrosis is present.

Anticoagulation therapy with warfarin sodium may enhance the release of atheromatous plaque emboli, thereby increasing the risk of complications from systemic cholesterol microembolization, including the "purple toes syndrome." Discontinuation of warfarin sodium therapy is recommended when such phenomena are observed.

Systemic atheroemboli and cholesterol microemboli can present with a variety of signs and symptoms including purple toes syndrome, livedo reticularis, rash, gangrene, abrupt and intense pain in the leg, foot, or toes, foot ulcers, myalgia, penile gangrene, abdominal pain, flank or back pain, hematuria, renal insufficiency, hypertension, cerebral ischemia, spinal cord infarction, pancreatitis, symptoms simulating polyarteritis, or any other sequelae of vascular compromise due to embolic occlusion. The most commonly involved visceral organs are the kidneys followed by the pancreas, spleen, and liver. Some cases have progressed to necrosis or death.

Purple toes syndrome is a complication of oral anticoagulation characterized by a dark, purplish or mottled color of the toes, usually occurring between 3 to 10 weeks, or later, after the initiation of therapy with warfarin or related compounds. Major features of this syndrome include purple color of plantar surfaces and sides of the toes that blanches on moderate pressure and fades with elevation of the legs; pain and tenderness of the toes; waxing and waning of the color over time. While the purple toes syndrome is reported to be reversible, some cases progress to gangrene or necrosis which may require debridement of the affected area, or may lead to amputation.

A severe elevation (>50 seconds) in activated partial thromboplastin time (aPTT) with a PT/INR in the desired range has been identified as an indication of increased risk of postoperative hemorrhage.

The decision to administer anticoagulants in the following conditions must be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the benefits:

***Lactation:** Warfarin sodium appears in the milk of nursing mothers in an inactive form. Infants nursed by warfarin sodium treated mothers had no change in prothrombin times (PTs). Effects in premature infants have not been evaluated.*

Severe to moderate hepatic or renal insufficiency.

***Infectious diseases or disturbances of intestinal flora:** sprue, antibiotic therapy.*

***Trauma** which may result in internal bleeding.*

***Surgery or trauma** resulting in large exposed raw surfaces.*

Indwelling catheters.

Severe to moderate hypertension.

***Known or suspected deficiency in protein C mediated anticoagulant response:** Hereditary or acquired deficiencies of protein C or its cofactor, protein S, have been associated with tissue necrosis following warfarin administration. Not all patients with these conditions develop necrosis, and tissue necrosis occurs in patients without these deficiencies. Inherited resistance to activated protein C has been described in many patients with venous thromboembolic disorders but has not yet been evaluated as a risk factor for tissue necrosis. The risk associated with these conditions, both for recurrent thrombosis and for adverse reactions, is difficult to evaluate since it does not appear to be the same for everyone. Decisions about testing and therapy must be made on an individual basis. It has been reported that concomitant anticoagulation therapy with heparin for 5 to 7 days during initiation of therapy with warfarin sodium may minimize the incidence of tissue necrosis. Warfarin therapy should be discontinued when warfarin is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation.*

***Miscellaneous:** polycythemia vera, vasculitis, and severe diabetes.*

Minor and severe allergic/hypersensitivity reactions and anaphylactic reactions have been reported.

In patients with acquired or inherited warfarin resistance, decreased therapeutic responses to warfarin sodium have been reported. Exaggerated therapeutic responses have been reported in other patients.

Patients with congestive heart failure may exhibit greater than exected PT/INR response to warfarin sodium, thereby requiring more frequent laboratory monitoring, and reduced doses of warfarin sodium.

Concomitant use of anticoagulants with streptokinase or urokinase is not recommended and may be hazardous. (Please note recommendations accompanying these preparations.)

PRECAUTIONS:

Periodic determination of PT/INR or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional PT/INR determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken irregularly. The following factors are listed for reference; however, other factors may also affect the anticoagulant response.

Drugs may interact with warfarin sodium through pharmacodynamic or pharmacokinetic mechanisms. Pharmacodynamic mechanisms for drug interactions with warfarin sodium are synergism (impaired hemostasis, reduced clotting factor synthesis), competitive antagonism (vitamin K), and altered physiologic control loop for vitamin K metabolism (hereditary resistance). Pharmacokinetic mechanisms for drug interactions with warfarin sodium are mainly enzyme induction, enzyme inhibition, and reduced plasma protein binding. It is important to note that some drugs may interact by more than one mechanism.

The following factors, alone or in combination, may be responsible for INCREASED PT/INR response:

Endogenous Factors:

blood dyscrasias-see CONTRAINDICATIONS	hepatic disorders: infectious hepatitis
cancer	jaundice
collagen vascular disease	hyperthyroidism
congestive heart failure	poor nutritional state
diarrhea	steatorrhea
elevated temperature	vitamin K deficiency

Exogenous Factors:

Potential drug interactions with warfarin sodium are listed below by drug class and by specific drugs.

Classes of Drugs	
Adrenergic Stimulants, Central	Gastrointestinal, Ulcerative Colitis Agents
Alcohol Abuse Reduction Preparations	Gout Treatment Agents
Analgesics	Hemorrheologic Agents
Anesthetics, Inhalation	Hepatotoxic Drugs
Antiarrhythmics*	Hyperglycemic Agents
Antibiotics*	Hypertensive Emergency Agents
Aminoglycosides (oral)	Hypnotics*
Cephalosporins, parenteral	Hypolipidemics*
Macrolides	Monoamine Oxidase Inhibitors
Miscellaneous	Narcotics, prolonged
Penicillins, intravenous, high dose	Nonsteroidal Anti-Inflammatory Agents
Quinolones (fluoroquinolones)	Psychostimulants
Sulfonamides, long acting	Pyrazolones
Tetracyclines	Salicylates
Anticoagulants	Selective Serotonin Reuptake Inhibitors
Anticonvulsants*	Steroids, Adrenocortical*
Antidepressants	Steroids, Anabolic (17-Alkyl Testosterone Derivatives)
Antimalarial Agents	Thrombolytics
Antineoplastics*	Thyroid Drugs
Antiparasitic/Antimicrobials	Tuberculosis* Agents*
Antiplatelet Drugs/Effects	Uricosuric Agents
Antithyroid Drugs*	Vaccines
Beta-Adrenergic Blockers	
Bromelains	
Cholelitholytic Agents	
Diabetes Agents, Oral	

Miscellaneous: polycythemia vera, vasculitis, and severe diabetes.

Minor and severe allergic/hypersensitivity reactions and anaphylactic reactions have been reported.

In patients with acquired or inherited warfarin resistance, decreased therapeutic responses to warfarin sodium have been reported. Exaggerated therapeutic responses have been reported in other patients.

Patients with congestive heart failure may exhibit greater than expected PT/INR response to warfarin sodium, thereby requiring more frequent laboratory monitoring, and reduced doses of warfarin sodium.

Concomitant use of anticoagulants with streptokinase or urokinase is not recommended and may be hazardous. (Please note recommendations accompanying these preparations.)

PRECAUTIONS:

Periodic determination of PT/INR or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional PT/INR determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken irregularly. The following factors are listed for reference; however, other factors may also affect the anticoagulant response.

Drugs may interact with warfarin sodium through pharmacodynamic or pharmacokinetic mechanisms. Pharmacodynamic mechanisms for drug interactions with warfarin sodium are synergism (impaired hemostasis, reduced clotting factor synthesis), competitive antagonism (vitamin K), and altered physiologic control loop for vitamin K metabolism (hereditary resistance). Pharmacokinetic mechanisms for drug interactions with warfarin sodium are mainly enzyme induction, enzyme inhibition, and reduced plasma protein binding. It is important to note that some drugs may interact by more than one mechanism.

The following factors, alone or in combination, may be responsible for INCREASED PT/INR response:

Endogenous Factors:

blood dyscrasias-see CONTRAINDICATIONS	hepatic disorders:
cancer	infectious hepatitis
collagen vascular disease	jaundice
congestive heart failure	hyperthyroidism
diarrhea	poor nutritional state
elevated temperature	steatorrhea
	vitamin K deficiency

Exogenous Factors:

Potential drug interactions with warfarin sodium are listed below by drug class and by specific drugs.

Classes of Drugs	
Adrenergic Stimulants, Central	Gastrointestinal, Ulcerative Colitis Agents
Alcohol Abuse Reduction Preparations	Gout Treatment Agents
Analgesics	Hemorrheologic Agents
Anesthetics, Inhalation	Hepatotoxic Drugs
Antiarrhythmics*	Hyperglycemic Agents
Antibiotics*	Hypertensive Emergency Agents
Aminoglycosides (oral)	Hypnotics*
Cephalosporins, parenteral	Hypolipidemics*
Macrolides	Monoamine Oxidase Inhibitors
Miscellaneous	Narcotics, prolonged
Penicillins, intravenous, high dose	Nonsteroidal Anti-Inflammatory Agents
Quinolones (fluoroquinolones)	Psychostimulants
Sulfonamides, long acting	Pyrazolones
Tetracyclines	Salicylates
Anticoagulants	Selective Serotonin Reuptake Inhibitors
Anticonvulsants*	Steroids, Adrenocortical*
Antidepressants	Steroids, Anabolic (17-Alkyl Testosterone Derivatives)
Antimalarial Agents	Thrombolytics
Antineoplastics*	Thyroid Drugs
Antiparasitic/Antimicrobials	Tuberculosis Agents*
Antiplatelet Drugs/Effects	Uricosuric Agents
Antithyroid Drugs*	Vaccines
Beta-Adrenergic Blockers	Vitamins*
Bromelains	
Cholelitholytic Agents	
Diabetes Agents, Oral	
Diuretics*	
Fungal Medications, Systemic*	
Gastric Acidity and Peptic Ulcer Agents*	

(Over)

Specific Drugs Reported

acetaminophen	methimazole*
alcohol*	methyldopa
allopurinol	methylphenidate
aminosalicylic acid	methylsalicylate ointment (topical)
amiodarone HCl	metronidazole
aspirin	miconazole
azithromycin	moniczine hydrochloride*
cefamandole	nalidixic acid
cefazolin	naproxen
cefoperazone	neomycin
cefotetan	norfloxacin
cefoxitin	ofloxacin
ceftriaxone	olsalazine
chenodiol	omeprazole
chloramphenicol	oxaprozin
chloral hydrate*	oxymetholone
chlorpropamide	parpwetine
cholestyramine*	penicillin G, intravenous
cimetidine	pentoxifylline
ciprofloxacin	phenylbutazone
clarithromycin	phenytoin*
clofibrate	piperacillin
cyclophosphamide*	piroxicam
danazol	prednisone*
dextran	propafenone
dextrothyroxine	propoxyphene
diazoxide	propranolol
diclofenac	propylthiouracil*
dicumarol	quinidine
diflunisal	quinine
disulfiram	ranitidine*
doxycycline	sertraline
erythromycin	simvastatin
ethacrynic acid	stanozolol
fenoprofen	streptokinase
fluconazole	sulfamethizole
fluorouracil	sulfamethoxazole
fluoxetine	sulfamethoxazole
fluvoxamine	sulfinpyrazone
glucagon	sulfisoxazole
halothane	sulindac
heparin	tamoxifen
ibuprofen	tetracycline
ifosfamide	thyroid
indomethacin	ticarcillin
influenza virus vaccine	ticlopidine
itraconazole	tissue plasminogen activator (t-PA)
ketoprofen	tolbutamide
ketorolac	trimethoprim/sulfamethoxazole
levamisole	urokinase
levothyroxine	valproate
liothyronine	vitamin E
lovastatin	warfarin sodium overdosage
mefenamic acid	

also: other medications affecting blood elements which may modify hemostasis

dietary deficiencies
prolonged hot weather
unreliable PT/INR determinations

*Increased and decreased PT/INR responses have been reported.

The following factors, alone or in combination, may be responsible for DECREASED PT/INR response:

Endogenous Factors:

edema	hereditary coumarin resistance	hyperlipemia
hypothyroidism	nephrotic syndrome	

Exogenous Factors:

Potential drug interactions with warfarin sodium are listed below by drug class and by specific drugs

Classes of Drugs

Adrenal Cortical Steroid Inhibitors	Enteral Nutritional Supplements
Antacids	Fungal Medications, Systemic*
Antianxiety Agents	Gastric Acidity and Peptic Ulcer Agents*
Antiarrhythmics*	
Antibiotics*	Hypnotics*
Anticonvulsants*	Hypolipidemics*
Antidepressants*	Immunosuppressives
Antihistamines	Oral Contraceptives, Estrogen Containing
Antineoplastics*	
Antipsychotic Medications	Steroids, Adrenocortical*
Antithyroid Drugs*	Tuberculosis Agents*
Barbiturates	Vitamins*
Diuretics*	

Specific Drugs Reported

alcohol*	methimazole*
aminoglutethimide	moniczine hydrochloride*
amobarbital	nafcillin
azathioprine	paraldehyde
butabarbital	pentobarbital
butalbital	phenobarbital
carbamazepine	phenytoin*
chloral hydrate*	prednisone*
chlordiazepoxide	primidone
chlorthalidone	propylthiouracil*
cholestyramine*	ranitidine*
corticotropin	rifampin
cortisone	secobarbital
cyclophosphamide*	spironolactone
dicloxacillin	sucralfate
ethchlorvynol	trazodone
glutethimide	vitamin C (high dose)
griseofulvin	vitamin K
haloperidol	warfarin sodium underdosage
meprobamate	
6-mercaptopurine	

also: diet high in vitamin K

unreliable PT/INR determinations

* Increased and decreased PT/INR responses have been reported.

Because a patient may be exposed to a combination of the above factors, the net effect of warfarin sodium on PT/INR response may be unpredictable. More frequent PT/INR monitoring is therefore advisable. Medications of unknown interaction with coumarins are best regarded with caution. When these medications are started or stopped, more frequent PT/INR monitoring is advisable.

It has been reported that concomitant administration of warfarin and ticlopidine may be associated with cholestatic hepatitis.

Effect on Other Drugs:

Coumarins may also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (phenytoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

Special Risk Patients:

Warfarin sodium is a narrow therapeutic range (index) drug, and caution should be observed when warfarin sodium is administered to certain patients such as the elderly or debilitated or when administered in any situation or physical condition where added risk of hemorrhage is present.

Intramuscular (I.M.) injections of concomitant medications should be confined to the upper extremities which permits easy access for manual compression, inspections for bleeding and use of pressure bandages.

Caution should be observed when warfarin sodium is administered concomitantly with nonsteroidal anti-inflamma-

also: diet high in vitamin K

unreliable PT/INR determinations

* *Increased and decreased PT/INR responses have been reported.*

Because a patient may be exposed to a combination of the above factors, the net effect of warfarin sodium on PT/INR response may be unpredictable. More frequent PT/INR monitoring is therefore advisable. *Medications of unknown* interaction with coumarins are best regarded with caution. When these medications are started or stopped, more frequent PT/INR monitoring is advisable.

It has been reported that concomitant administration of warfarin and ticlopidine may be associated with cholestatic hepatitis.

Effect on Other Drugs:

Coumarins may also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (phenytoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

Special Risk Patients:

Warfarin sodium is a narrow therapeutic range (index) drug, and caution *should be observed when* warfarin sodium is administered to certain patients such as the elderly or debilitated or when administered in any situation or physical condition where added risk of *hemorrhage is present.*

Intramuscular (I.M.) injections of concomitant medications should be confined to the upper extremities which permits easy access for manual compression, inspections for bleeding and use of pressure bandages.

Caution should be observed *when warfarin sodium is administered* concomitantly with nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, to be certain that no change in anticoagulation dosage is required. In addition to *specific drug interactions that might affect* PT/INR, NSAIDs, including aspirin, can inhibit platelet aggregation, and can cause gastrointestinal bleeding, peptic ulceration and/or perforation.

Acquired or inherited warfarin resistance *should be suspected if large daily doses of* warfarin sodium are required to maintain a patient's PT/INR within a normal therapeutic range.

Information for Patients:

The objective of anticoagulant therapy *is to decrease the clotting ability of the blood so that thrombosis is prevent*ed, while avoiding spontaneous bleeding. Effective therapeutic levels with minimal complications are in part dependent upon cooperative and well-instructed patients who communicate effectively with their physician. Patients should be advised: Strict adherence to prescribed dosage schedule is necessary. Do not take or discontinue any *other medication*, including salicylates (e.g., aspirin and topical analgesics) and other over-the-counter medications except on advice of the physician. Avoid alcohol consumption. Do not take warfarin sodium during pregnancy and do not become pregnant while taking it (see **CONTRAINDICATIONS**). Avoid any activity or sport that may result in traumatic injury. Prothrombin time tests and regular visits to physician or clinic are needed to monitor therapy. Carry identification stating that warfarin sodium is being taken. If the prescribed dose of warfarin sodium is forgotten, notify the physician immediately. Take the dose as soon as possible on the same day but do not take *a double dose of* warfarin sodium the next day to make up for missed doses. The amount of vitamin K in food may affect therapy with warfarin sodium. Eat a normal, balanced diet maintaining *a consistent amount of vitamin K.* Avoid drastic changes in dietary habits, such as eating large amounts of green leafy vegetables. Contact physician to report any illness, such as diarrhea, infection or fever. *Notify physician immediately if any unusual bleeding or symptoms occur.* Signs and symptoms of bleeding include: pain, swelling or discomfort, prolonged bleeding from cuts, increased menstrual flow or vaginal bleeding, *nosebleeds*, bleeding of gums from brushing, unusual bleeding or bruising, red or dark brown urine, red or tar black stools, headache, dizziness, or weakness. If therapy with warfarin sodium is discontinued, *patients should be cautioned that* the anticoagulant effects of warfarin sodium may persist for about 2 to 5 days.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenicity and mutagenicity studies have not been performed with warfarin sodium. The reproductive effects of warfarin sodium have not been evaluated.

Use in Pregnancy:

Pregnancy Category X. See **CONTRAINDICATIONS**.

Pediatric Use:

Safety and effectiveness in pediatric patients below the age of *18 have not been established, in randomized, con*trolled clinical trials. However, the use of warfarin sodium in pediatric patients is well-documented for the prevention and treatment of thromboembolic events. *Difficulty achieving and maintaining* therapeutic PT/INR ranges in the pediatric patient has been reported. More frequent PT/INR determinations are recommended because of possible changing warfarin requirements.

ADVERSE REACTIONS:

Potential adverse reactions to warfarin sodium may include:

• Fatal or nonfatal hemorrhage from any tissue or organ. This is a consequence *of the anticoagulant effect. The signs*, symptoms, and severity will vary according to the location and degree or extent of the bleeding. Hemorrhagic complications may present as paralysis; paresthesia; headache, chest, abdomen, joint, *muscle or other pain*; dizziness; shortness of breath, difficult breathing or swallowing; unexplained swelling; weakness; hypotension; or unexplained shock. Therefore, the possibility of *hemorrhage should be considered in evaluating* the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with PT/INR. (See **OVERDOSAGE-Treatment.**)

• Bleeding which occurs when the PT/INR is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g., tumor, ulcer, etc.

• *Necrosis of skin and other tissues.* (See **WARNINGS.**)

• Adverse reactions reported infrequently include: hypersensitivity/allergic reactions, systemic cholesterol microembolization, purple toes syndrome, hepatitis, *cholestatic hepatic injury*, jaundice, elevated liver enzymes, vasculitis, edema, fever, rash, dermatitis, including bullous eruptions, urticaria, abdominal pain including cramping, flatulence/bloating, fatigue, lethargy, malaise, asthenia, nausea, vomiting, diarrhea, pain, headache, dizziness, taste perversion, pruritis, alopecia, cold intolerance, and paresthesia including feeling cold and chills.

Rare events of tracheal or tracheobronchial calcification have been reported *in association with long-term warfarin* therapy. The clinical significance of this event is unknown.

Priapism has been associated with anticoagulant administration, however, a causal relationship has not been established.

OVERDOSAGE:

Signs and Symptoms:

Suspected or overt abnormal bleeding (e.g., appearance *of blood in* stools or urine, hematuria, excessive menstrual bleeding, melena, petechiae, excessive bruising or persistent oozing from superficial injuries) are early manifestations of anticoagulation *beyond a safe and satisfactory* level.

Treatment:

Excessive anticoagulation, with or without bleeding, may be controlled by discontinuing warfarin sodium therapy and *if necessary*, by administration of oral or parenteral vitamin K_1. (Please see recommendations accompanying vitamin K_1 preparations prior to use.)

Such use of vitamin K_1 reduces response to subsequent *warfarin sodium* therapy. Patients may return to a pretreatment thrombotic status following the rapid reversal of a prolonged PT/INR. Resumption of warfarin sodium administration reverses the *effect of vitamin* K_1 *and a therapeutic* PT/INR can again be obtained by careful dosage adjustment. If rapid anticoagulation is indicated, heparin may be preferable for initial therapy.

If minor bleeding progresses to major bleeding, give 5 to 25 mg (rarely up to 50 mg) parenteral vitamin K_1. In emergency situations of severe hemorrhage, clotting factors can be returned to normal by administering 200 to 500 mL of fresh whole blood or fresh frozen plasma, or by giving *commercial Factor IX complex.*

A risk of hepatitis and other viral diseases is associated with the use of these blood products; Factor IX complex is also associated with an increased risk of thrombosis. Therefore, these preparations should be used only in exceptional or life-threatening bleeding episodes secondary to warfarin sodium overdosage.

Purified Factor IX preparations should not be used because they cannot increase the levels of prothrombin, Factor *VII and Factor X which are also depressed along with the levels of Factor IX as a result of warfarin sodium treatment.* Packed red blood cells may also be given if significant blood loss has occurred. Infusions of blood or plasma should be monitored carefully to avoid precipitating pulmonary edema in elderly patients or patients with heart disease.

DOSAGE AND ADMINISTRATION:

The dosage and administration of warfarin sodium must be individualized for each patient according to the particular patient's responsiveness to the drug. The dosage should be adjusted based upon the patient's PT/INR. (See **Laboratory Control** below for full discussion on INR.)

Venous Thromboembolism (including pulmonary embolism):

Available clinical evidence indicates that an INR of 2.0 to 3.0 is sufficient for prophylaxis and treatment of venous thromboembolism and minimizes *the risk of hemorrhage* associated with higher INRs.

Atrial Fibrillation:

Five recent clinical trials evaluated the effects of warfarin in patients with non-valvular atrial fibrillation (AF). Meta-analysis findings of these studies revealed that the effects of warfarin in reducing thromboembolic events including stroke were similar at either moderately high INR (2.0 to 4.5) or low INR (1.4 to 3.0). There was a significant reduction in *minor* bleeds at the low INR. Similar data from clinical studies in valvular atrial fibrillation patients are not available. The trials in non-valvular atrial fibrillation support the American College of Chest Physicians' (ACCP) rec*ommendation* that an INR of 2.0 to 3.0 be used for long-term warfarin therapy in appropriate AF patients.

Purified Factor IX preparations should not be used because they cannot increase the levels of prothrombin. Factor VII and Factor X which are also depressed along with the levels of Factor IX as a result of warfarin sodium treatment. Packed red blood cells may also be given if significant blood loss has occurred. Infusions of blood or plasma should be monitored carefully to avoid precipitating pulmonary edema in elderly patients or patients with heart disease.

DOSAGE AND ADMINISTRATION:

The dosage and administration of warfarin sodium must be individualized for each patient according to the particular patient's responsiveness to the drug. The dosage should be adjusted based upon the patient's PT/INR. (See **Laboratory Control** below for full discussion on INR.)

Venous Thromboembolism (including pulmonary embolism):

Available clinical evidence indicates that an INR of 2.0 to 3.0 is sufficient for prophylaxis and treatment of venous thromboembolism and minimizes the risk of hemorrhage associated with higher INRs.

Atrial Fibrillation:

Five recent clinical trials evaluated the effects of warfarin in patients with non-valvular atrial fibrillation (AF). Meta-analysis findings of these studies revealed that the effects of warfarin in reducing thromboembolic events including stroke were similar at either moderately high INR (2.0 to 4.5) or low INR (1.4 to 3.0). There was a significant reduction in minor bleeds at the low INR. Similar data from clinical studies in valvular atrial fibrillation patients are not available. The trials in non-valvular atrial fibrillation support the American College of Chest Physicians' (ACCP) recommendation that an INR of 2.0 to 3.0 be used for long-term warfarin therapy in appropriate AF patients.

Post-Myocardial Infarction:

In post myocardial infarction patients, warfarin sodium therapy should be initiated early (2 to 4 weeks post-infarction) and dosage should be adjusted to maintain an INR of 2.5 to 3.5 long-term. The recommendation is based on the results of the WARIS study in which treatment was initiated 2 to 4 weeks after the infarction. In patients thought to be at an increased risk of bleeding complications or on aspirin therapy, maintenance of warfarin sodium therapy at the lower end of this INR range is recommended.

Mechanical and Bioprosthetic Heart Valves:

In patients with mechanical heart valve(s), long-term prophylaxis with warfarin to an INR of 2.5 to 3.5 is recommended. In patients with bioprosthetic heart valve(s), based on limited data, the American College of Chest Physicians recommends warfarin therapy to an INR of 2.0 to 3.0 for 12 weeks after valve insertion. In patients with additional risk factors such as atrial fibrillation or prior thromboembolism, consideration should be given for longer term therapy.

Recurrent Systemic Embolism:

In cases where the risk of thromboembolism is great, such as in patients with recurrent systemic embolism, a higher INR may be required.

An INR of greater than 4.0 appears to provide no additional therapeutic benefit in most patients and is associated with a higher risk of bleeding.

Initial Dosage:

The dosing of warfarin sodium must be individualized according to patient's sensitivity to the drug as indicated by the PT/INR. Use of a large loading dose may increase the incidence of hemorrhagic and other complications, does not offer more rapid protection against thrombi formation, and is not recommended. Low initiation doses are recommended for elderly and/or debilitated patients and patients with potential to exhibit greater than expected PT/INR response to warfarin sodium (see **PRECAUTIONS**). It is recommended that warfarin sodium therapy be initiated with a dose of 2 to 5 mg per day with dosage adjustments based on the results of PT/INR determinations.

Maintenance:

Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of Therapy:

The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Missed Dose:

The anticoagulant effect of warfarin sodium persists beyond 24 hours. If the patient forgets to take the prescribed dose of warfarin sodium at the scheduled time, the dose should be taken as soon as possible on the same day. The patient should not take the missed dose by doubling the daily dose to make up for missed doses, but should refer back to his or her physician.

Laboratory Control:

The PT reflects the depression of vitamin K dependent Factors VII, X and II. There are several modifications of the one-stage PT and the physician should become familiar with the specific method used in his laboratory. The degree of anticoagulation indicated by any range of PTs may be altered by the type of thromboplastin used; the appropriate therapeutic range must be based on the experience of each laboratory. The PT should be determined daily after the administration of the initial dose until PT/INR results stabilize in the therapeutic range. Intervals between subsequent PT determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin sodium in order to maintain the individual within the therapeutic range. Acceptable intervals for PT/INR determinations are normally within the range of one to four weeks after a stable dosage has been determined. To ensure adequate control, it is recommended that additional PT tests are done when other warfarin products are interchanged with warfarin sodium and also if other medications are coadministered with warfarin sodium (see **PRECAUTIONS**).

Different thromboplastin reagents vary substantially in their sensitivity to sodium warfarin-induced effects on PT. To define the appropriate therapeutic regimen it is important to be familiar with the sensitivity of the thromboplastin reagent used in the laboratory and its relationship to the International Reference Preparation (IRP), a sensitive thromboplastin reagent prepared from human brain.

A system of standardizing the PT in oral anticoagulant control was introduced by the World Health Organization in 1983. It is based upon the determination of an International Normalized Ratio (INR) which provides a common basis for communication of PT results and interpretations of therapeutic ranges. The INR system of reporting is based on a logarithmic relationship between the PT ratios of the test and reference preparation. The INR is the PT ratio that would be obtained if the International Reference Preparation (IRP), which has an ISI of 1.0, were used to perform the test. Early clinical studies of oral anticoagulants, which formed the basis for recommended therapeutic ranges of 1.5 to 2.5 times control mean normal PT, used sensitive human brain thromboplastin. When using the less sensitive rabbit brain thromboplastins commonly employed in PT assays today, adjustments must be made to the targeted PT range that reflect this decrease in sensitivity.

The INR can be calculated as: $INR=(\text{observed PT ratio})^{ISI}$

where the ISI (International Sensitivity Index) is the correction factor in the equation that relates the PT ratio of the local reagent to the reference preparation and is a measure of the sensitivity of a given thromboplastin to reduction of vitamin K-dependent coagulation factors; the lower the ISI, the more "sensitive" the reagent and the closer the derived INR will be to the observed PT ratio.[1]

The proceedings and recommendations of the 1992 National Conference on Antithrombotic Therapy [2 to 4] review and evaluate issues related to oral anticoagulant therapy and the sensitivity of thromboplastin reagents and provide additional guidelines for defining the appropriate therapeutic regimen.

The conversion of the INR to PT ratios for the less-intense (INR 2.0 to 3.0) and more intense (INR 2.5 to 3.5) therapeutic range recommended by the ACCP for thromboplastins over a range of ISI values is shown in Table 2.[5]

TABLE 2
Relationship Between INR and PT Ratios for Thromboplastins With Different ISI Values (Sensitivities)

	PT Ratios				
	ISI 1.0	ISI 1.4	ISI 1.8	ISI 2.3	ISI 2.8
INR=2.0-3.0	2.0-3.0	1.6-2.2	1.5-1.8	1.4-1.6	1.3-1.5
INR=2.5-3.5	2.5-3.5	1.9-2.4	1.7-2.0	1.5-1.7	1.4-1.6

Treatment During Dentistry and Surgery:

The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. PT/INR determination is recommended just prior to any dental or surgical procedure. In patients undergoing minimal invasive procedures who must be anticoagulated prior to, during, or immediately following these procedures, adjusting the dosage of warfarin sodium to maintain the PT/INR at the low end of the therapeutic range may safely allow for continued anticoagulation. The operative site should be sufficiently limited and accessible to permit the effective use of local procedures for hemostasis. Under these conditions, dental and minor surgical procedures may be performed without undue risk of hemorrhage. Some dental or surgical procedures may necessitate the interruption of warfarin sodium therapy. When discontinuing warfarin sodium even for a short period of time, the benefits and risks should be strongly considered.

Conversion From Heparin Therapy:

Since the anticoagulant effect of warfarin sodium is delayed, heparin is preferred initially for rapid anticoagulation. Conversion to warfarin sodium may begin concomitantly with heparin therapy or may be delayed 3 to 6 days. To ensure continuous anticoagulation, it is advisable to continue full dose heparin therapy and that warfarin sodium therapy be overlapped with heparin for 4 to 5 days, until warfarin sodium has produced the desired therapeutic response as determined by PT/INR. When warfarin sodium has produced the desired PT/INR or prothrombin activity, heparin may be discontinued.

Warfarin sodium may increase the aPTT test, even in the absence of heparin. During initial therapy with warfarin sodium, the interference with heparin anticoagulation is of minimal clinical significance.

As heparin may affect the PT/INR, patients receiving both heparin and warfarin sodium should have blood for PT/INR

physicians, surgeons and dentists. PT/INR determination is recommended just prior to a [illegible] procedure. In patients undergoing minimal invasive procedures who must be anticoagulated prior to, during, or immediately following these procedures, adjusting the dosage of warfarin sodium to maintain the PT/INR at the low end of the therapeutic range may safely allow for continued anticoagulation. The operative site should be sufficiently familiar and accessible to permit the effective use of local procedures for hemostasis. Under these conditions, dental and minor surgical procedures may be performed without undue risk of hemorrhage. Some dental or surgical procedures may necessitate the interruption of warfarin sodium therapy. When discontinuing warfarin sodium even for a short period of time, the benefits and risks should be strongly considered.

Conversion From Heparin Therapy:

Since the anticoagulant effect of warfarin sodium is delayed, heparin is preferred initially for rapid anticoagulation. Conversion to warfarin sodium may begin concomitantly with heparin therapy or may be delayed 3 to 5 days. To ensure continuous anticoagulation, it is advisable to continue full dose heparin therapy and that warfarin sodium therapy be overlapped with heparin for 4 to 5 days, until warfarin sodium has produced the desired therapeutic response as determined by PT/INR. When warfarin sodium has produced the desired PT/INR or prothrombin activity, heparin may be discontinued.

Warfarin sodium may increase the aPTT test, even in the absence of heparin. During initial therapy with warfarin sodium, the interference with heparin anticoagulation is of minimal clinical significance.

As heparin may affect the PT/INR, patients receiving both heparin and warfarin sodium should have blood for PT/INR determination drawn at least:

- 5 hours after the last IV bolus dose of heparin, or
- 4 hours after cessation of a continuous IV infusion of heparin, or
- 24 hours after the last subcutaneous heparin injection.

HOW SUPPLIED:

Warfarin Sodium Tablets, USP are available as:

1 mg: Pink, oval, flat-faced, beveled-edge, scored tablet. Debossed with 555/831 on the scored side and Barr on the other side. Available in bottles of:

100	NDC 0555-0831-02
500	NDC 0555-0831-04
1000	NDC 0555-0831-05

2 mg: Lavender, oval, flat-faced, beveled-edge, scored tablet. Debossed with 555/869 on the scored side and Barr on the other side. Available in bottles of:

100	NDC 0555-0869-02
500	NDC 0555-0869-04
1000	NDC 0555-0869-05

2.5 mg: Green, oval, flat-faced, beveled-edge, scored tablet. Debossed with 555/832 on the scored side and Barr on the other side. Available in bottles of:

100	NDC 0555-0832-02
500	NDC 0555-0832-04
1000	NDC 0555-0832-05

4 mg: Blue, oval, flat-faced, beveled-edge, scored tablet. Debossed with 555/874 on the scored side and Barr on the other side. Available in bottles of:

100	NDC 0555-0874-02
1000	NDC 0555-0874-05

5 mg: Peach, oval, flat-faced, beveled-edge, scored tablet. Debossed with 555/833 on the scored side and Barr on the other side. Available in bottles of:

100	NDC 0555-0833-02
500	NDC 0555-0833-04
1000	NDC 0555-0833-05

7.5 mg: Yellow, oval, flat-faced, beveled-edge, scored tablet. Debossed with 555/834 on the scored side and Barr on the other side. Available in bottles of:

100	NDC 0555-0834-02
1000	NDC 0555-0834-05

10 mg: White, oval, flat-faced, beveled-edge, scored tablet. Debossed with 555/835 on the scored side and Barr on the other side. Available in bottles of:

100	NDC 0555-0835-02
500	NDC 0555-0835-04

Dispense with a child-resistant closure in a light, light-resistant container as defined in the USP.

Protect from light.

Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

REFERENCES:

1. Poller, L.: Laboratory Control of Anticoagulant Therapy. Seminars in Thrombosis and Hemostasis, Vol. 12, No. 1, pp. 13-19, 1986.

2. Hirsh, J.: Is the Dose of Warfarin Prescribed by American Physicians Unnecessarily High? *Arch Int Med*, Vol. 147, pp. 769-771, 1987.

3. Cook, D.J., Guyatt, H.G., Laupacis, A., Sackett, D.L.: Rules of Evidence and Clinical Recommendations on the Use of Antithrombotic Agents. *Chest* ACCP Consensus Conference on Antithrombotic Therapy. *Chest*, Vol. 102(Suppl), pp. 305S-311S, 1992.

4. Hirsh, J., Dalen, J., Deykin, D., Poller, L.: Oral Anticoagulants Mechanism of Action, Clinical Effectiveness, and Optimal Therapeutic Range. *Chest* ACCP Consensus Conference on Antithrombotic Therapy *Chest*, Vol. 102(Suppl), pp. 312S-326S, 1992.

5. Hirsh, J., M.D., F.C.C.P.: Hamilton Civic Hospitals Research Center, Hamilton, Ontario, Personal Communication.

MANUFACTURED BY
BARR LABORATORIES, INC.
POMONA, NY 10970

BR-831, 869, 832, 874, 833, 834, 835
Revised SEPTEMBER 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040145

BIOEQUIVALENCE DISSOLUTION REVIEWS

JAN 2 1997

FILE COPY

Warfarin Sodium Tablets
1, 2, 2.5, 4, 5, 7.5 & 10 mg
ANDA #40-145
Reviewer: L. Chuang

Barr Laboratories, Inc.
Pomona, NY
Submission Date:
November 1, 1996

Review of an Bioequivalence Amendment

Background:

The original ANDA submitted on 05/10/95 included results of two bioequivalence studies on the 2 mg (2x2 mg) and 10 mg (1x10 mg) strength products, dissolution data and waiver request for the 1, 2.5, 4, 5, 7.5 mg strength products.

A review of the original submission was completed 11/27/95 and 3 deficiencies were found. The firm responded to these deficiencies in an amendment submitted on 05/16/96 which included information of lot sizes of the 2 mg and 10 mg test products, assay methodology for dissolution testing and results of 2 additional bioequivalence studies on the 2.5 mg (2x2.5 mg) and 5 mg (1x5 mg) tablets respectively.

The review completed on 10/24/96 found 2 additional deficiencies in that amendment which were related to the potencies and dissolution tests of the test and reference drugs used in the bioequivalence studies for the 2.5 mg and 5 mg strengths. The current amendment is in response to those 2 deficiencies.

Review:

Comparative dissolution tests were conducted by the firm on its Warfarin Sodium tablets, 2.5 mg and 5 mg, compared to Coumadin^{R} tablets, 2.5 mg and 5 mg, respectively, manufactured by Dupont Merck Pharmaceuticals. The method, results, content uniformity and potency are presented below:

In Vitro Dissolution Testing
Drug (Generic Name): Warfarin Sodium Dose Strength: 2.5 mg and 5 mg ANDA No.: 40-145 Firm: Barr Laboratories, Inc. Submission Date: 11/1/96
I. Conditions for Dissolution Testing:

USP XXIII Apparatus: Paddle RPM: 50
No. Units Tested: 12
Medium: Deaerated Water Volume: 900 ml
Tolerance: NLT 80% of warfarin (Q) in 30 minutes (USP 23 specification)
Reference Drug: Coumadin[R] Tablets (Dupont)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Batch # 4R83224 Strength (mg): 2.5			Reference Product Batch # EJN319A Strength (mg): 2.5		
	Mean %	Range	%CV	Mean %	Range	%CV
5	45		11.1	26		13.6
10	81		8.7	84		17.5
20	101		1.5	103		3.5
30	101		1.7	104		3.6

Test Product: content uniformity of 98.3% (1.8%CV), and potency of 98.3%
Reference Product: content uniformity of 99.8% (1.6%CV), and potency of 99.4%

Sampling Times (Minutes)	Test Product Batch # 4R83325 Strength (mg): 5			Reference Product Batch # EJJ234A Strength (mg): 5		
	Mean %	Range	%CV	Mean %	Range	%CV
5	42		14.2	33		8.7
10	74		11.7	62		6.1
20	99		2.8	101		3.4
30	101		2.5	102		2.4

Test Product: content uniformity of 99.7% (2.01%CV), and potency of 100.0%
Reference Product: content uniformity of 99.3% (0.93%CV), and potency of 99.6%

Comment:

The dissolution test and potency data submitted by the firm are acceptable.

Recommendation:

1. All four bioequivalence studies conducted by Barr Laboratories. Inc. on its Warfarin Sodium 2 mg, 2.5 mg, 5 mg and 10 mg tablets. Lot #4R86911, #4R83224. #4R83325 and #4R83512 respectively. comparing to Coumadin[R] 2 mg, 2.5 mg, 5 mg, and 10 mg tablets. lot #EFF122A, #EJN319A and #EJJ234A and #EFF101A respectively, manufactured by Dupont Merck Pharmaceutical Co., in fasting volunteers, have been found acceptable by the Division of Bioequivalence. These studies demonstrated that Barr's warfarin sodium 2 mg, 2.5 mg, 5 mg, and 10 mg tablets are bioequivalent to the reference product. Coumadin[R] 2 mg, 2.5 mg, 5 mg, and 10 mg tablets respectively, manufactured by Dupont Merck Pharmaceutical Co., when administered under fasting condition.

2. The dissolution tests conducted by Barr Laboratories, Inc. on its 1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg and 10 mg tablets, lot #4R83123, #4R86911, #4R83224, #4R87427, #4R83325, #4R83426, and #4R83512 respectively, have been found acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of deaerated water at 37° C using USP 23 apparatus 2 (paddle) at 50 rpm. The test products should meet the following USP 23 specification:

> Not less than 80% of the labeled amount of warfarin sodium in the dosage form is dissolved in 30 minutes.

3. The waivers of in vivo bioequivalence study requirements for Barr's warfarin sodium tablets, 1 mg, 4 mg, and 7.5 mg, are granted. The firm's warfarin sodium tablets, 1 mg, 4 mg, and 7.5 mg, are therefore deemed bioequivalent to Coumadin[R] tablets, 1 mg, 4 mg, and 7.5 mg, respectively, manufactured by Dupont Merck Pharmaceutical Co.

L. Huang 12/31/96

Lin-whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG 12/31/96

Concur: 1/2/97
Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

cc: ANDA 40-145 (original, duplicate), Chuang HFD-652 (Huang), Drug File. Division File.

First Draft. LWC. 12/30/96. c:\wpfiles\40145a.n96
Final Pink. LWC. 12/31/96. x:\new\firmsam\barr\ltrs&rev\40145a.n96

OCT 24 1996

FILE COPY

Warfarin Sodium Tablets
1, 2, 2.5, 4, 5, 7.5 & 10 mg
ANDA #40-145
Reviewer: L. Chuang

Barr Laboratories, Inc.
Pomona, NY
Submission Date:
May 16, 1996

Review of an Amendment containing Two Bioequivalence Studies, Dissolution Data and Waiver Request

Background:

The original ANDA submitted on 05/10/95 contained results of two bioequivalence studies on the 2 mg (2x2 mg) and 10 mg (1x10 mg) strength products, dissolution data and waiver request for the 1, 2.5, 4, 5, 7.5 strength products.

Three deficiencies were described in the review completed 11/27/95 which were related to the lot sizes of both test products, the assay methodology described in the dissolution tests, and the waiver request.

The firm responded with information on the lot size of both test products (tablets) and dissolution assay method and results of **two additional** bioequivalence studies on the 2.5 mg (2x2.5 mg) and 5 mg strength products to support the waiver request for the 1, 4, and 7.5 mg strength products..

The two bioequivalence studies are reviewed below:

Bioequivalence Study -- 2 X 2.5 mg

The objective of this study is to compare the relative bioavailability of warfarin sodium following a single dose of two of the firm's warfarin sodium 2.5 mg tablets with that of two of Coumadin® 2.5 mg tablets, manufactured by DuPont Merck in healthy adult male volunteers under fasting conditions.

The clinical study was conducted at during February 17-27 and March 17-27, 1996 with as investigators. The analytical study was conducted at during the time period of April 5-May 1, 1996 with s the analytical investigator. The statistical analysis was conducted by

The design was a single-dose, 2-way crossover in fasting male volunteers. The protocol and the informed consent form were approved by the
on January 31, 1996.

Twenty-six non-smoking male volunteers, 18-38 years old, were enrolled. At enrollment, within 21 days prior to period 1 dosing, they all weighed within ±10% of normal weight for their height and frame, had an acceptable medical history, medication history, physical examination, sitting blood pressure, heart rate, ECG, clinical laboratory evaluation, a non-reactive HIV 1 & 2 antibody screen, and negative screens for hepatitis B surface antigen and drugs of abuse.

Volunteers were instructed of the following restrictions:

1. not to take any non-prescription medication within 7 days prior to period 1 dosing
2. not to take any prescription medication within 14 days prior to period 1 dosing
3. not to take any caffeine, xanthine or alcohol-containing products within 48 hours prior to each dosing and during blood collection period
4. report to the investigator of the intake of any concomitant medications during the period of the study

The prothrombin time of each subject was monitored on study day -1 and day 28 between 18-24 hours prior to dosing and after each dosing at 24 and 96 hours.

Subjects were confined to the clinical facility from 10 hours before to 24 hours after dosing. After an overnight fast of 10 hr, each subject received one of the following treatments with 240 mL of water:

Treatment A - Test Drug: Warfarin Sodium tablets, 2 x 2.5 mg, Barr Laboratories, Inc., lot #4R83224, potency 97.8%, , lot size tablets

Treatment B - Reference Drug: Coumadin^{R} tablets, 2 x 2.5 mg, Dupont Merck lot #EJN319A, expires 10/98, potency not given

After a 29-day washout, each subject was crossed over to the alternative treatment.

Blood samples were obtained in EDTA vacutainers within 1 hour prior to dosing and at 10, 20, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, 14, 24, 48, 72, 96, 144, 192, and 240 hours. Plasma samples were prepared, frozen, and stored until the completion of the study. They were then packaged in dry ice and transported overnight to the analytical site.

Subjects were not allowed to recline for the first four hours postdose or engage in any strenuous activity during confinement.

Subjects fasted for 4 hours after dosing. No fluids were allowed for 1 hour before and 2 hours after dosing except those taken with the drug. At 2 hours after dosing, 240 mL of water was given to each subject and standard fluid and food were served thereafter.

For safety monitoring, blood pressure and heart rate were measured prior to dosing and at 12, 24, and 240 hours after dosing. Within 14 days after the last blood collection, each subject completed an exit procedure including general observations, physical examination, blood pressure, heart rate and body temperature evaluation.

Analytical Method -- **Not for Release through FOI**:

The mean plasma concentrations of warfarin at each sampling time point after both treatments and the mean pharmacokinetic parameters are presented below in Table 1.

Table 1: Mean (C.V.%) Plasma Warfarin Concentrations (ng/mL) at Each Sampling Time Point and the Mean Pharmacokinetic Parameters (n = 25 - 2 X 2.5 mg Tablets)

Time (hour)	Barr (Treatment A)	Dupont Merck (Treatment B)
0	0.724 (500)	0
0.17	117.68 (62)	73.84 (52)
0.33	409.88 (39)	356.94 (42)
0.50	525.48 (26)	503.04 (27)
0.75	540.68 (18)	513.96 (19)
1.00	496.64 (19)	485.80 (18)
1.50	438.16 (18)	439.28 (18)
2.00	417.76 (17)	416.40 (18)
3.00	390.20 (17)	397.76 (20)
4.00	369.16 (16)	380.36 (21)
6.00	308.04 (15)	315.52 (20)
8.00	297.96 (17)	297.52 (18)
10.00	283.84 (17)	291.20 (16)
14.00	254.08 (15)	255.56 (16)
24.00	210.12 (18)	218.76 (16)
48.00	131.67 (21)	137.60 (16)
72.00	90.18 (23)	91.60 (18)
96.0	63.52 (24)	64.06 (22)
144.0	38.42 (25)	37.17 (27)
192.0	25.77 (29)	26.39 (29)
240.0	20.56 (29)	20.52 (27)

AUC_{0-t} (ng*hr/mL)	20628.16 (17)	20907.20 (15)
AUC_{0-inf} (ng*hr/mL)	23041.04 (18)	23310.83 (17)
C_{max} (ng/mL)	583.84 (17)	568.44 (16)
$LNAUC_{0-t}$	9.9201, 20334.38[a]	9.9368, 20676.44[a]
$LNAUC_{0-inf}$	10.0299, 22695.72[a]	10.0426, 22984.80[a]
LNC_{max}	6.3562, 576.04[a]	6.3304, 561.37[a]
T_{max} (hour)	0.665 (39)	0.846 (84)
$T_{1/2}$ (hour)	77.914 (30)	79.10 (36)

a = geometric mean

Analysis of Variance was performed using SAS GLM procedure. The model included sequence, subject, subject within sequence, treatment and period as factors. The sequence effect was tested using the subjects within sequence effect as the error term. The treatment and period effect were tested against the residual mean square error.

No significant effects were detected for non-transformed and log-transformed AUC_{0-t}, AUC_{0-inf}, or C_{max}.

The LS means of the non-transformed and log-transformed pharmacokinetic parameters, ratios of these means and the 90% confidence intervals of test product versus reference product are presented in Table 2.

Table 2: Statistical Analysis - Warfarin Sodium - 2x2.5 mg (n=25)

Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
AUC_{0-t}	20601.06	20889.89	0.99	(0.957; 1.015)
$LNAUC_{0-t}$	9.920068 (20334.38[a])	9.93676 (20676.64[a])	0.98[b]	(0.954; 1.014)
AUC_{0-inf}	23025.89	23303.73	0.99	(0.958; 1.018)
$LNAUC_{0-inf}$	10.02993 (22695.72[a])	10.04259 (22984.80[a])	0.99[b]	(0.958; 1.018)
C_{max}	583.97	568.09	1.03	(0.979; 1.076)
LNC_{max}	6.356181 (576.04[a])	6.330375 (561.37[a])	1.03[b]	(0.977; 1.078)

a = Geometric Mean
b = Ratio of Geometric Means

Comments:

1. The potency of the reference drug used in this bioequivalence study was not reported.

2. The computation of all AUC0-t, $AUC_{0\text{-}inf}$, and C_{max} and their 90% confidence intervals have been confirmed by the reviewer.

Bioequivalence Study -- 1 X 5 mg

The objective of this study is to compare the relative bioavailability of warfarin sodium following a single dose of the firm's warfarin sodium 5 mg tablets with that of Coumadin^R 5 mg tablets, manufactured by DuPont Merck in healthy adult male volunteers under fasting conditions.

The clinical study was conducted at during January 6-16 and February 3-13, 1996 with as investigators. The analytical study was conducted at during the time period of February 16-March 18, 1996 with , the analytical investigator. The statistical analysis was conducted by

The design was a single-dose, 2-way crossover in fasting male volunteers. The protocol and the informed consent form were approved by the on December 26, 1995.

Twenty-six non-smoking male volunteers, 18-38 years old, were enrolled. The screening procedure, restrictions, and safety monitoring were the same as those in the previous study.

Subjects were confined to the clinical facility from 10 hours before to 24 hours after dosing. After an overnight fast of 10 hr, each subject received one of the following treatments with 240 mL of water:

Treatment A - Test Drug: Warfarin Sodium tablets, 1 x 5 mg, Barr Laboratories, Inc., lot #4R83225, potency 96.7%, , lot size

Treatment B - Reference Drug: Coumadin^R tablets, 1 x 5 mg, Dupont Merck lot #EJJ234A, expires 07/98, potency not given.

After a 28-day washout, each subject was crossed over to the alternative treatment.

The blood sampling schedule, plasma (561.37) ing, and dose administration were the same as (576.04)

a = Geometric Mean
b = Ratio of Geometric Means

Analytical Method -- **Not for Release through FOI**:

Table 3: Mean (C.V.%) Plasma Warfarin Concentrations (ng/mL) at Each Sampling Time Point and the Mean Pharmacokinetic Parameters (n = 25 - 1x5 mg Tablet)

Time (hour)	Barr (Treatment A)	Dupont Merck (Treatment B)
0	0	0
0.17	138.49 (78)	101.52 (94)
0.33	465.40 (38)	318.92 (54)
0.50	579.76 (14)	489.76 (26)
0.75	559.48 (13)	556.32 (17)
1.00	527.40 (17)	518.76 (13)
1.50	461.56 (17)	468.44 (14)
2.00	444.28 (16)	435.88 (15)
3.00	400.16 (16)	408.92 (12)
4.00	383.68 (16)	388.00 (15)
6.00	323.40 (20)	317.40 (13)
8.00	295.80 (17)	298.76 (17)
10.00	287.52 (17)	284.92 (13)
14.00	269.80 (17)	264.40 (14)
24.00	211.88 (19)	210.88 (16)
48.00	138.26 (20)	140.76 (17)
72.00	98.47 (26)	96.89 (24)
96.0	71.16 (21)	67.50 (19)
144.0	38.87 (23)	40.51 (23)
192.0	27.27 (32)	24.97 (23)
240.0	18.58 (26)	17.34 (26)
AUC_{0-t} (ng*hr/mL)	21565.81 (19)	21280.60 (15)
AUC_{0-inf} (ng*hr/mL)	23243.92 (18)	22790.44 (15)
C_{max} (ng/mL)	618.04 (17)	600.12 (18)
$LNAUC_{0-t}$	9.9620, 21204.92[a]	9.9547, 21050.82[a]
$LNAUC_{0-inf}$	10.0373, 22863.64[a]	10.0235, 22551.23[a]
LNC_{max}	6.4128, 609.58[a]	6.3794, 589.58[a]
T_{max} (hour)	0.608 (36)	0.776 (37)
$T_{1/2}$ (hour)	61.446 (13)	59.16 (13)

a = geometric mean

Analysis of Variance was performed using SAS GLM procedure. The model included sequence. subject, subject within sequence. treatment and period as factors. The sequence effect was tested using the subjects within sequence effect as the error term. The treatment and period effect were tested against the residual mean square error.

No significant effects were detected for non-transformed and log-transformed AUC_{0-t}, AUC_{0-inf}, or C_{max}.

The LS means of the non-transformed and log-transformed pharmacokinetic parameters, ratios of these means and the 90% confidence intervals of test product versus reference product are presented in Table 4.

Table 4: Statistical Analysis - Warfarin Sodium - 1x5 mg (n=25)

Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
AUC_{0-t}	21525.80	21261.64	1.01	(0.984: 1.041)
$LNAUC_{0-t}$	9.961989 (21204.92[a])	9.954695 (21050.82[a])	1.01[b]	(0.980; 1.036)
AUC_{0-inf}	23205.77	22776.60	1.02	(0.990: 1.048)
$LNAUC_{0-inf}$	10.03730 (22863.64[a])	10.02354 (22551.23[a])	1.01[b]	(0.985: 1.044)
C_{max}	616.75	599.76	1.03	(0.977: 1.080)
LNC_{max}	6.412774 (609.58[a])	6.379417 (589.58[a])	1.03[b]	(0.984: 1.086)

a = Geometric Mean
b = Ratio of Geometric Means

Comments:

1. The potency of the reference drug used in this bioequivalence study was not reported.

2. The computation of all AUC0-t, AUC_{0-inf}, and C_{max} and their 90% confidence intervals have been confirmed by the reviewer.

General Deficiencies:

1. The potencies of both reference drugs, Coumadin[R] 2.5 mg and 5 mg tablets. lot

#EJN319A and #EJJ234A respectively, were not reported.

2. The firm did not submit any dissolution data comparing the same lots of test and reference drugs used for above bioequivalence studies.

Recommendation:

1. Both bioequivalence studies conducted by Barr Laboratories, Inc. on its Warfarin Sodium 2.5 mg and 5 mg tablets, Lot #4R83224 and #4R83225 respectively, comparing to Coumadin[R] 2.5 mg and 5 mg tablets, lot #EJN319A and #EJJ234A respectively, manufactured by Dupont Merck Pharmaceutical Co. in fasting volunteers, have been found incomplete due to deficiency #1.

2. The firm should conduct comparative dissolution tests comparing Barr's Warfarin Sodium tablets, 2.5 mg and 5 mg, lot #4R83224 and #4R83325 respectively, to Coumadin[R] tablet, 2.5 mg and 5 mg, lot #EFF122A and #EJJ234A respectively. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° using USP 23 apparatus 2 (peddle) at 50 rpm. The test products should meet the following specifications:

   Not less thar of the labeled amount of warfarin in the dosage form is dissolved in 30 minutes.

3. The waiver of <u>in vivo</u> bioequivalence study requirements for the firm's Warfarin Sodium 1 mg, 4 mg, and 7.5 mg tablets can not be granted per 21 CFR320.22(d)(2) at present due to the deficiencies.

The above deficiencies and recommendations should be forwarded to the firm.

L. Chuang 10/24/96

Lin-whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED RMHATRE
FT INITIALED RMHATRE Ramakant M. Mhatre 10/24/96

cc: ANDA 40-145 (original, duplicate), Chuang HFD-652 (Huang), Drug File. Division File.

First Draft LWC. 09/16/96. c:\wpfiles\40145sww.596
Final Pink. LWC, 10/24/96, x:\new\firmsam\barr\ltrs&rev\40145sw.596

NOV 27 1995

Warfarin Sodium Tablets
1, 2, 2,5, 4, 5, 7.5 & 10 mg
ANDA #40-145
Reviewer: L. Chuang
WP# x:\new\firmsam\ltrs&rev\40145sdw.595

Barr Laboratories. Inc.
Chesterfield. Missouri
Submission Date:
May 10. 1995

Review of Two Bioequivalence Studies, Dissolution Data and Waiver Request

Introduction:

Warfarin Sodium is an anticoagulant drug. The drug acts by inhibiting the synthesis of vitamin K dependent coagulation factors. The resultant in vivo effect is a sequential depression of Factors VII, IX, X, and II activities. The degree of depression depends on the administered dose. It is indicated for the prophylaxis and/or treatment of venous thrombosis.

Warfarin is a racemic mixture of S and L enantiomers. The S enantiomer is 3-5 times more potent than the R enantiomer. The oral absorption of warfarin sodium is complete. Maximum plasma concentrations occur in 1 to 9 hours. It is approximately 97% bound to plasma albumin. An anticoagulation effect generally occurs within 24 hours. However, peak anticoagulant effect may be delayed 72 to 96 hours and its duration of action may persist for 4 to 5 days. The half-life of warfarin sodium is about 2.5 days and it is metabolized in the liver to inactive metabolites.

The dosage of the drug is dependent on the response of the patient. Dosage should be controlled by determination of one stage prothrombin time. Most patients are satisfactorily maintained at 2-10 mg/day.

The listed reference drug of warfarin sodium is Coumadin® tablets, 1, 2, 2.5, 4, 5, 7.5 and 10 mg, manufactured by DuPont Merck Pharmaceutical Co..

Bioequivalence Study -- 2 X 2 mg

The objective of this study is to compare the relative bioavailability of warfarin sodium following a single dose of the firm's 2 mg tablets with that of Coumadin® 2 mg tablets, manufactured by DuPont Merck in healthy adult male volunteers under fasting conditions.

The clinical study was conducted at during October 16-26 and November 13-23, 1994 with as investigators. The analytical study was conducted at in during the time period of January 26 - February 20, 1995 with

The design was a single-dose, 2-way crossover in fasting male volunteers. The protocol and the informed consent form were approved by the
on September 8, 1994.

Twenty-six (24 plus 2 alternates) male volunteers, 18-37 years old, were enrolled. Each volunteer completed the screening process within 14 days prior to period 1 dosing. The inclusion criteria were:

1. male, 18-40 years old, within ± 10% of ideal weight for height and frame
2. good health as determined by medical history, physical examination, and laboratory tests (hematology, serum chemistry, urinalysis)
3. negative screening of HIV 1 & 2 antibody and hepatitis B surface antigen
4. negative urine drug screen of ethyl alcohol, amphetamine, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, opiates and phencyclidine
5. comprehension of and ability to sign the consent form

The exclusion criteria were:

1. recent history of alcoholism or drug abuse
2. requirement of medication for the treatment of any disorder
3. clinical laboratory test results outside acceptable range and deemed clinically significant
4. history of allergy to warfarin sodium or related drugs, and any clinically significant allergy
5. clinically significant illness within 4 weeks prior to period 1 dosing
6. current tobacco product users
7. intake of any drugs within 30 days that are known to be toxic to major organs
7. donating more than 150 mL of blood or receiving any investigational drugs within 30 days prior to period 1 dosing
8. reporting the intake of prescription medication or had plasmapheresis within 14 days prior to period 1 dosing

Volunteers were instructed of the following restrictions:

1. not to take any non-prescription medication within 7 days of period 1 dosing
2. not to take any aspirin or any NSAIDS within 72 hours of period 1 dosing and at any time during the study
3. not to take any caffeine, xanthine or alcohol-containing products within 48 hours prior to each dosing and during blood collection period
4. report to the investigator of the intake of any concomitant

medications during the period of the study

The prothrombin time of each subject was monitored on study day -1 between 18-22 hours prior to dosing and after each dosing at 24 and 96 hours.

Subjects were confined to the clinical facility from 10 hours before to 24 hours after dosing. After an overnight fast of 10 hr, each subject received one of the following treatments with 240 mL of water:

Treatment A - Test Drug: Warfarin Sodium tablets, 2 x 2 mg, Barr Laboratories, Inc., lot #4R86911, potency 101.1%, manufacturing date 07/12/94, lot size not given

Treatment B - Reference Drug: Coumadin® tablets, 2 x 2 mg, Dupont Merck lot #EFF122A, expires 05/96, potency 98.9%.

After a 28-day washout, each subject was crossed over to the alternative treatment.

Blood samples were obtained in EDTA vacutainers within 1 hour prior to dosing and at 10, 20, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 24, 48, 72, 96, 144, 192, and 240 hours. Plasma samples were prepared, frozen, and stored until the completion of the study. They were then packaged in dry ice and transported overnight to the analytical site.

Subjects were not allowed to recline for the first four hours postdose or engage in any strenuous activity during confinement.

Subjects fasted for 4 hours after dosing. No fluids were allowed for 1 hour before and 2 hours after dosing except those taken with the drug. At 4 hours after dosing, 240 mL of water was given to each subject and standard fluid and food were served thereafter.

For safety monitoring, blood pressure and heart rate were measured prior to dosing and at 12, 24, and 240 hours after dosing. Within 14 days after the last blood collection, each subject completed an exit procedure including general observations, physical examination, blood pressure, heart rate and body temperature evaluation.

Analytical Method -- **Not for Release through FOI:**

Results:

The results of safety monitoring of prothrombin time, blood pressure and heart rate were reviewed by the the medical investigator, and the results were either within the reference range or considered not clinically significant.

The study was completed in 25 of the 26 subjects enrolled, subject #6 failed to report for period 2 and was dropped from the study. There were 4 subjects who deviated from the protocol and took a multivitamin (#2), vitamin C (#4) and ibuprofen (#16), all at -6 days and #22 took a multivitamin at -5 days. Two cases of minor problems were resolved prior to period 1 dosing and no medications were needed, i.e., subject #1 had rhinitis on day -12 and #11 had muscle aches during days 8-26 before the start of the study. All these deviations were considered acceptable by the medical investigator.

Thirty-one (31) adverse events were reported in 16 subjects, 10 subjects reported 14 events during treatment A and 12 subjects reported 17 events during treatment B. Only 9 of these events were possibly or probably related to the administered drug, they were dyspepsia, flatus (2 events), headache (5 events) and scratchy throat.

The results of exit procedures did not reveal any clinically significant abnormalities.

The plasma samples from 24 subjects (first 12 subjects from each sequence who completed the study) were assayed for warfarin. Among the 1056 study samples analyzed, 11 were repeated. Two (2) were repeated due to anomalous values, each was repeated twice and median values were used in the final report.

The mean plasma concentrations of warfarin at each sampling point after both treatments and the mean pharmacokinetic parameters are presented below in Table 1.

Table 1: Mean (C.V.%) Plasma Warfarin Concentrations (ng/mL) at Each Sampling Time Point and the Mean Pharmacokinetic Parameters (n = 24 - 2 X 2 mg Tablets)

Time (hour)	Barr (Treatment A)	Dupont Merck (Treatment B)
0	0	0
0.17	90.69 (64)	109.09 (82)
0.33	328.42 (49)	333.62 (45)
0.50	418.93 (31)	417.58 (22)
0.75	395.04 (23)	407.75 (20)
1.00	360.37 (21)	380.29 (21)
1.50	326.71 (23)	343.67 (18)

2.00	310.92 (20)	325.17 (20)
3.00	290.46 (21)	301.54 (20)
4.00	269.92 (20)	281.04 (19)
6.00	219.33 (18)	229.29 (19)
8.00	205.42 (16)	213.12 (18)
10.00	200.12 (16)	209.21 (18)
12.00	192.50 (18)	202.87 (22)
14.00	182.54 (15)	192.96 (19)
24.00	156.12 (18)	163.68 (22)
48.00	107.80 (22)	105.20 (21)
72.00	74.72 (22)	74.33 (23)
96.0	53.41 (23)	54.30 (24)
144.0	33.92 (30)	36.13 (28)
192.0	22.97 (32)	22.68 (28)
240.0	16.26 (44)	17.55 (36)
AUC_{0-t} (ng*hr/mL)	16263.12 (19)	16710.33 (20)
AUC_{0-inf} (ng*hr/mL)	18310.33 (20)	18806.33 (22)
C_{max} (ng/mL)	457.25 (23)	465.00 (21)
$LNAUC_{0-t}$	9.679776, 15990.9[a]	9.705314, 16404.5[a]
$LNAUC_{0-inf}$	9.797043, 17980.5[a]	9.820654, 18410.1[a]
LNC_{max}	6.101001, 446.3[a]	6.120309, 455.0[a]
T_{max} (hour)	0.6313 (60)	0.6346 (56)
$T_{1/2}$ (hour)	78.9087 (14)	80.4417 (14)

a = geometric mean

Analysis of Variance was performed using SAS GLM procedure. The model included sequence, subject, subject within sequence, treatment and period as factors. The sequence effect was tested using the subjects within sequence effect as the error term. The treatment and period effect were tested against the residual mean square error.

Only significant period effects were detected for AUC_{0-t}, AUC_{0-inf}, $LNAUC_{0-t}$, and $LNAUC_{0-inf}$ (p=0.0001-0.0005) with period 2 higher than period 1.

The LS means of the non-transformed and log-transformed pharmacokinetic parameters, ratios of these means and the 90% confidence intervals of test product versus reference product are presented in Table 2.

Table 2: Statistical Analysis - Warfarin Sodium - 2x2 mg (n=24)

Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
AUC_{0-t}	16263.1	16710.3	0.97	(0.949; 0.998)
$LNAUC_{0-t}$	9.679776 (15990.9[a])	9.705314 (16404.5[a])	0.97[b]	(0.949; 1.000)
AUC_{0-inf}	18310.3	18806.3	0.97	(0.947; 1.000)
$LNAUC_{0-inf}$	9.797043 (17980.5[a])	9.820654 (18410.1[a])	0.98[b]	(0.950; 1.000)
C_{max}	457.25	465.00	0.98	(0.922; 1.170)
LNC_{max} .	6.01001 (446.3[a])	6.120309 (455.01[a])	0.98[b]	(0.887; 1.080)

a = Geometric Mean
b = Ratio of Geometric Means

Comments:

The firm did not provide the lot size of the test product used in this bioequivalence study.

Bioequivalence Study -- 1 X 10 mg

The objective of this study is to compare the relative bioavailability of warfarin sodium following a single dose of the firm's 10 mg tablet with that of Coumadin® 10 mg tablet, manufactured by Dupont Merck in healthy adult male volunteers under fasting conditions.

The clinical study was conducted at during the time period of October 9-22 and November 6-19, 1994 with as investigators. The analytical study was conducted at in during the time period of January 11 - February 1, 1995 with as the analytical

investigator.

The design was a single-dose, 2-way crossover study in fasting male volunteers. The protocol and the informed consent form were approved by the
on October 6, 1994.

Twenty-six (24 plus 2 alternates) male volunteers, 18-39 years old, were enrolled. Each volunteer completed the screening process within 14 days prior to period 1 dosing. The inclusion and exclusion criteria were the same as those reported in the previous study.

All subjects were subjected to the same restrictions as reported in the previous study. The prothrombin time of each subject was monitored on study day -1 between 18-22 hours prior dosing and after each dosing at 24 and 96 hours.

Subjects were confined to the clinical facility from 10 hours before to 24 hours after dosing. After an overnight fast of 10 hr, each subject received one of the following treatments with 240 mL of water:

Treatment A - Test Drug: Warfarin Sodium tablets, 1 x 10 mg, Barr Laboratories, Inc., lot #4R83512, potency 101.7%, manufacturing date 07/08/94, lot size not given

Treatment B - Reference Drug: Coumadin® tablets, 1 x 10 mg, Dupont Merck lot #EFF101A, expires 04/96, potency 98.9%.

The washout period (28 days), blood sample collection schedule, plasma storage, subjects' restriction on fluid, food and physical activity, and safety monitoring were the same as those reported for the previous study.

Analytical Method -- **Not for Release through FOI:**

Results:

The results of safety monitoring of prothrombin time, blood pressure and heart rate were reviewed by the the medical investigator, and the results were either within the reference range or considered not clinically significant. Subject #4 had a blood pressure reading of 128/44 at 12 hours postdose during period 2 (treatment B).

The study was completed in 25 of the 26 subjects enrolled, subject #21 was dropped from the study prior to period 2 dosing due to bilateral otitis and pharyngitis and was given oral antibiotics. His failure to complete the study was not related to study medication.

Before study initiation, two subjects deviated from protocol, #12 took 400 mg of Ibuprofen at day -7 and #18 took a multivitamin tablet on day -6. These deviations were considered acceptable by the medical investigator.

During the course of the study, 4 subjects deviated from the protocol, #6 took vitamin C on days 17-18, #9 took acetaminophen on days 2-3 and Walfed cold medicine on days 3-5, #20 was treated for laceration with topical medications of betadine, 1% xylocaine, epinephrine, and bacitracin, and #23 took Sudafed on days 2-6. These medications were considered by the investigator not to effect the integrity of the study.

Twenty-two (22) adverse events were reported in 11 subjects, 8 subjects reported 12 events during treatment A and 7 subjects reported 10 events during treatment B. Only 5 of these events were possibly or probably related to the drug administered, they were all related to headache. Other adverse complaints included conjunctivitis, edema, fracture of the finger, hot flushes, laceration of left eyebrow, antecubital pain, pharyngitis, head congestion, chest congestion and rhinitis.

The results of exit procedures did not reveal any clinically significant abnormalities.

The plasma samples from 24 subjects (first 12 subjects from each sequence who completed study) were assayed for warfarin. Among the 1056 study samples analyzed, 12 were repeated. Three (3) were repeated due to anomalous values, each was repeated twice and median values were used in the final report.

The mean plasma concentrations of warfarin at each sampling point after both treatments and the mean pharmacokinetic parameters are presented below in Table 3.

Table 3: Mean (C.V.%) Plasma Warfarin Concentrations (ng/mL) at

Each Sampling Time Point and the Mean Pharmacokinetic Parameters (n = 24 - 1 X 10 mg Tablets)

Time (hour)	Barr (Treatment A)	Dupont Merck (Treatment B)
0	0	0
0.17	199.60 (73)	211.44 (84)
0.33	711.33 (55)	638.75 (59)
0.50	985.00 (39)	881.04 (46)
0.75	1054.37 (25)	984.33 (33)
1.00	1053.17 (13)	968.79 (24)
1.50	1006.08 (11)	970.50 (12)
2.00	934.96 (8.8)	923.83 (13)
3.00	875.50 (8.9)	897.62 (12)
4.00	829.87 (10)	828.67 (12)
6.00	705.00 (9.8)	715.12 (11)
8.00	682.70 (9.1)	697.75 (13)
10.00	639.25 (8.9)	649.50 (11)
12.00	605.83 (10)	612.67 (11)
14.00	575.62 (12)	571.54 (11)
24.00	479.04 (11)	477.83 (13)
48.00	289.92 (15)	299.04 (18)
72.00	193.00 (22)	195.33 (25)
96.00	135.46 (33)	120.67 (31)
144.00	64.33 (30)	63.90 (39)
192.00	38.29 (37)	37.05 (38)
240.00	25.75 (35)	25.10 (46)
312.00	15.38 (50)	15.47 (60)
AUC_{0-t} (ng*hr/mL)	44740.42 (15)	44211.83 (15)
AUC_{0-inf} (ng*hr/mL)	46612.75 (15)	46080.83 (19)
C_{max} (ng/mL)	1208.83 (17)	1179.79 (16)

$LNAUC_{0-t}$	10.6978, 44257.7[a]	10.6812, 43530.1[a]
$LNAUC_{0-inf}$	10.7383, 46089.1[a]	10.7211, 45303.6[a]
LNC_{max}	7.0844, 1193.2[a]	7.0615, 1166.2[a]
T_{max} (hour)	0.8296 (44)	1.0346 (65)
$T_{1/2}$ (hour)	71.9333 (30)	71.3167 (31)

a = geometric mean

Analysis of Variance was performed using SAS GLM procedure. The model included sequence, subject, subject within sequence, treatment and period as factors. The sequence effect was tested using the subjects within sequence effect as the error term. The treatment and period effect were tested against the residual mean square.

No significant effects were detected for any of the variables of any of the parameters.

The LS means of the non-transformed and log-transformed pharmacokinetic parameters, ratios of these means and the 90% confidence intervals of test product versus reference product are presented in Table 4.

Table 4: Statistical Analysis - Warfarin Sodium - 1x10 mg (n=24)

Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
AUC_{0-t}	44740.42	44211.83	1.01	(0.982; 1.04)
$LNAUC_{0-t}$	10.69778 (44257.7[a])	10.68121 (43530.1[a])	1.02[b]	(0.988; 1.05)
AUC_{0-inf}	46612.75	46080.83	1.01	(0.982; 1.04)
$LNAUC_{0-inf}$	10.73833 (46089.1[a])	10.72114 (45303.6[a])	1.02[b]	(0.989; 1.05)
C_{max}	1208.83	1179.79	1.02	(0.946; 1.10)
LNC_{max}	7.0844 (1193.21[a])	7.061469 (1166.16[a])	1.02[b]	(0.951; 1.10)

a = Geometric Mean
b = Ratio of Geometric Means

Comments:

1. Using the data provided on the sponsor's diskette, the reviewer confirmed the values for the means and confidence intervals of the non-transformed and log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} reported by the sponsor.

2. The firm did not provide the lot size of the test product used in this bioequivalence study.

3. The pharmacokinetics of warfarin seems to be dose independent as derived from the results of the two bioequivalence studies in this submission. The AUC_{0-inf} and C_{max} are both proportional to the administered dose as presented below in Table 5:

Table 5: Dose Proportionality of PK Parameters

Administered Dose	AUC_{0-inf}	C_{max}
4 mg	18558	461
10 mg	46347	1194
Ratio (10 mg/4 mg)	2.50	2.59

4. The labeling of Coumadin® does not contain any information related to the effect of food. Therefore, no food-related study is required.

Dissolution Testing:

Comparative dissolution tests were conducted by the firm on its Warfarin Sodium tablets, 1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg, and 10 mg, compared to Coumadin® tablets, 1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg, and 10 mg, respectively, manufactured by Dupont Merck Pharmaceuticals. The method and results are presented in Table 6.

Table 6 - In Vitro Dissolution Testing

Drug (Generic Name): Warfarin Sodium

Dose Strength: 1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg and 10 mg
ANDA No.: 40-145
Firm: Barr Laboratories, Inc.
Submission Date: 5/10/95

I. Conditions for Dissolution Testing:

USP XXIII Apparatus: Paddle RPM: 50
No. Units Tested: 12
Medium: Deaerated Water Volume: 1000 ml
Tolerance: NLT f warfarin (Q) in 30 minutes
Reference Drug: Coumadin® Tablets (Dupont)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Batch # 4R83123 Strength (mg): 1			Reference Product Batch # FB022A Strength (mg): 1		
	Mean %	Range	%CV	Mean %	Range	%CV
5	42.4		11.8	26.3		29.5
10	93.3		7.1	92.6		17.5
20	100.2		3.3	103.5		4.6
30	100.8		3.3	104.0		4.2

Sampling Times (Minutes)	Test Product Batch # 4R86911 Strength (mg): 2			Reference Product Batch # EFF122A Strength (mg): 2		
	Mean %	Range	%CV	Mean %	Range	%CV
5	35.8		13.7	29.0		16.0
10	70.0		13.2	79.6		19.4
20	105.2		1.9	102.0		2.9
30	105.7		2.2	101.9		2.7

Sampling Times (Minutes)	Test Product Batch # 4R83224 Strength (mg): 2.5			Reference Product Batch # EFB034A Strength (mg): 2.5		
	Mean %	Range	%CV	Mean %	Range	%CV
5	45.5		26.5	27.9		14.9
10	95.1		11.8	89.9		9.8
20	100.4		1.4	96.9		4.1
30	100.1		2.4	97.6		3.6

Sampling Times (Minutes)	Test Product Batch # 4R87427 Strength (mg): 4			Reference Product Batch # HA013B Strength (mg): 4		
	Mean %	Range	%CV	Mean %	Range	%CV
5	38.9		11.3	22.9		18.2
10	72.4		7.6	48.9		8.9
20	99.7		1.5	98.1		8.5
30	100.8		1.1	100.8		6.6

Sampling Times (Minutes)	Test Product Batch # 4R83325 Strength (mg): 5			Reference Product Batch # HEFA011A Strength (mg): 5		
	Mean %	Range	%CV	Mean %	Range	%CV
5	37.4		12.3	26.4		23.7
10	72.7		10.9	56.0		6.6
20	99.0		5.1	92.3		16.4
30	99.9		4.8	101.7		1.4

Sampling Times (Minutes)	Test Product Batch # 4R83426 Strength (mg): 7.5			Reference Product Batch # EE0226A Strength (mg): 7.5		
	Mean %	Range	%CV	Mean %	Range	%CV
5	37.8		13.1	32.5		16.2
10	90.2		13.1	62.0		11.8
20	103.2		1.9	95.7		6.6
30	103.3		2.0	98.6		4.2

Sampling Times (Minutes)	Test Product Batch # 4R83512 Strength (mg): 10			Reference Product Batch # EFE01A Strength (mg): 10		
	Mean %	Range	%CV	Mean %	Range	%CV
5	31.3		15.4	36.1		9.1
10	64.2		15.4	65.2		5.8
20	98.9		2.3	95.2		2.1
30	101.0		1.5	99.6		1.9

Comment:

The firm did not submit the assay methodology used for the dissolution test except quoting

Request for Waiver of Bioequivalence Testing for Wafarin Sodium Tablets, 1 mg, 2.5 mg 4 mg, 5 mg, and 7.5 mg

In support of this request , the firm has submitted, besides the

two *in vivo* bioequivalence studies and the above *in vitro* comparative dissolution tests, the following comparative formulations for all strengths of the firm's Warfarin Sodium Tablets in Table 6:

Table 6: Quantitative List of Components of Warfarin Sodium Tablet Manufactured by Barr Laboratories

	1 mg	2 mg	2.5 mg	4 mg	5 mg	7.5 mg	10 mg
Ingredients	mg/Tablet						
Warfarin Sodium*	1.00	2.00	2.50	4.00	5.00	7.50	10.00
Anhydrous Lactose**							
Pregelatinized Starch							
Hydroxypropyl Methylcellulose							
Magnesium Stearate							
D&C Red #6							
FD&C Blue #2							
FD&C Red #40							
FD&C Blue #1							
D&C Yellow #6							
D&C Yellow #10							
Total Weight	220.00	220.00	220.00	220.00	220.00	220.00	220.00

* = Weight adjusted according to the assay value
** = Weight adjusted for total weight
NP = Not present

Comments:

1. The ratio of lactose to the total weight varied between which is acceptable (see Table 7).

2. The ratio of the weight of each inactive ingredient to the total tablet weight of the 4 mg, 5 mg and 7.5 mg strengths is the same as that of the 10 mg tablet except the ratio for (see Table 7).

3. The ratio of the weight of each inactive ingredient to the total tablet weight of the 1 mg and 2.5 mg strengths is the

same as that of the 2 mg tablet except the ratios for . The ratio of total tablet weight is for the 2 mg tablet and for the 1 mg and 2.5 mg tablets. The ratio of to the total tablet weight is for the 2 mg tablet and for both 1 mg and 2.5 mg tablets. The ratio of to the total tablet weight is for both 1 mg and 2 mg tablets and for the 2.5 mg tablet (see Table 7).

Table 7: Percentage of Amount of Inactive Ingredients to Total Tablet Weight

	1 mg	2 mg	2.5 mg	4 mg	5 mg	7.5 mg	10 mg
Ingredients	Percent (%)						
Anhydrous Lactose**							
Pregelatinized Starch							
Hydroxypropyl Methylcellulose							
Magnesium Stearate							
D&C Red #6							
FD&C Blue #2							
FD&C Red #40							
FD&C Blue #1							
D&C Yellow #6							
D&C Yellow #10							

Deficiencies:

1. The firm should submit the lot sizes of both test products used in the two bioequivalence studies.

2. The firm should submit the assay methodology used in the dissolution tests, i.e.,

3. The firm should provide scientific evidence or documentation that the difference in the amount of between the test products used for the bioequivalence studies and the test products requesting waivers would not affect their comparative bioavailability.

Recommendation:

1. Both bioequivalence studies conducted by Barr Laboratories, Inc. on its Warfarin Sodium 2 mg and 10 mg tablets, Lot #4R8961 and #4R83512, comparing to Coumadin® 2 mg and 10 mg tablets, lot #EFF122A and #EFF101A respectively, manufactured by Dupont Merck Pharmaceutical Co. in fasting volunteers, have been found incomplete due to deficiency #1.

2. The dissolution tests conducted by Barr Laboratories, Inc. on its Warfarin Sodium tablets, 1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg and 10 mg, Lot #4R83123, #4R86911, #4R83224, #4R87427, #4R83325, #4R83426, and #4R83512 respectively, comparing to Coumadin® tablet, 1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg, and 10 mg respectively, manufactured by Dupont Merck Pharmaceutical Co., have been found incomplete by the Division of Bioequivalence due to deficiency #2.

3. The waiver of in vivo bioequivalence study requirements for the firm's Warfarin Sodium 1 mg, 2.5 mg, 4 mg, 5 mg, and 7.5 mg tablets can not be granted per 21 CFR320.22(d)(2) at present due to deficiency #3.

The above deficiencies and recommendations should be forwarded to the firm.

Lin-whei Chuang

Lin-whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED AJACKSON
FT INITIALED AJACKSON

cc: ANDA 40-145 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-652 (Chuang, Huang), Drug File, Division File.

First Draft 11/13/95
Pink Draft 11/22/95 x:\new\firmsam\ltrs&rev\40145sdw.595
Pink final 11/27/95 x:\new\firmsam\ltrs&rev\40145sdw.595